C-UK-H06049-29-P25395

Volume 99, Number 4, April 1992 BJOGAS 99(4) 275–354 1992 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

Edited by David B. Paintin

29

SUPER ARDUA

Published on behalf of the
Royal College of Obstetricians and Gynaecologists
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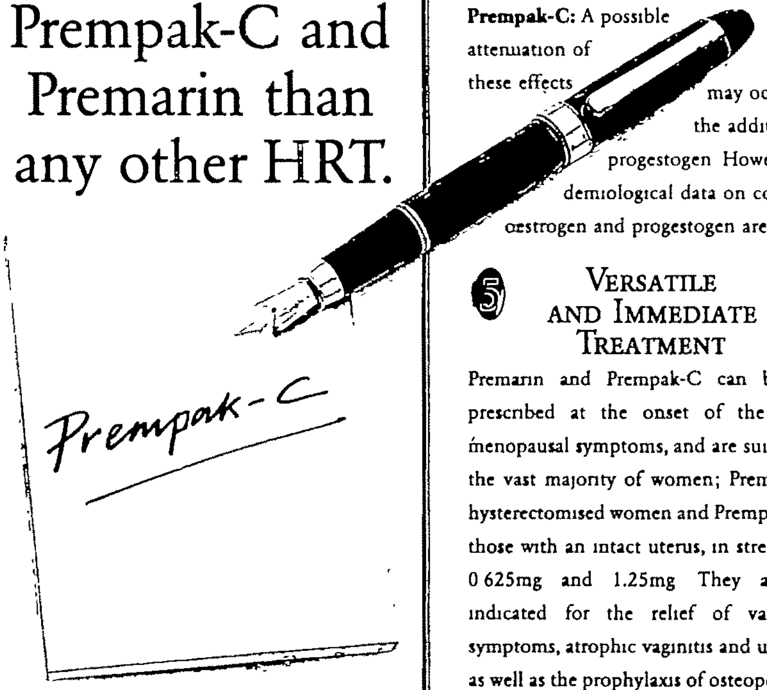
6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.



❶ 50 YEARS EXPERIENCE

Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products

❷ LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

❸ PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%[4]

❹ REDUCING CARDIOVASCULAR DISEASE RISKS

Premarin: A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users The most common form of oestrogen used in all these studies wa conjugated oestrogen, i e Premarin

Prempak-C: A possible attenuation of these effects may occur with the addition of a progestogen However, epidemiological data on combined oestrogen and progestogen are limite

❺ VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both b prescribed at the onset of the earlies menopausal symptoms, and are suitable fo the vast majority of women; Premarin fo hysterectomised women and Prempak-C fo those with an intact uterus, in strengths o 0 625mg and 1.25mg They are al indicated for the relief of vasomo symptoms, atrophic vaginitis and ureth as well as the prophylaxis of osteoporos women at risk.

❻ COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1 65 and Prempak-C costs £3.98, for 28 days of therapy[7]

PREMPAK-C
PREMARIN

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN* **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

DOSAGE AND ADMINISTRATION. Natural conjugated oestrogens 0 625mg - 1 25mg daily Continuous administration is recommended In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential

CONTRA-INDICATIONS. Known or suspected pregnancy and during lactation History of known or suspected cancer of the breast Oestrogen dependent neoplasia Undiagnosed abnormal genital bleeding Active thrombophlebitis or thromboembolic disorders Acute or chronic liver disease Rotor or Dubin-Johnson syndrome Severe cardiac or renal disease

WARNINGS AND PRECAUTIONS Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship It is not known whether concurrent progestogen influences this risk The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosus, porphyria, melanoma, epilepsy, migraine and asthma Use with caution in patients with pre existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop Certain endocrine and liver function tests may be affected Rarely idiosyncratic hypertension may occur Discontinue treatment prior to surgery or prolonged immobilisation Gallbladder disease Insulin requirements may be altered Premarin is not an oral contraceptive

SIDE EFFECTS. The following have been reported with oestrogen therapy premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps

PRODUCT LICENCE NUMBERS Premarin 0 625mg PL0011/0165 Premarin 1 25mg PL0011/0164 Premarin 2 5mg PL0011/0167 **BASIC NHS PRICE:** Premarin 0 625mg £1 65 (28 days) For full prescribing information please refer to data sheet

PREMPAK-C **USES** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

DOSAGE AND ADMINISTRATION· Natural conjugated oestrogens 0 625mg - 1 25mg daily and one norgestrel 0 15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy

CONTRA-INDICATIONS· As for Premarin

WARNINGS AND PRECAUTIONS As for Premarin Prempak-C is not an oral contraceptive

SIDE EFFECTS As for Premarin. Breakthrough bleeding and spotting Change in menstrual flow, dysmenorrhoea, amenorrhoea

PRODUCT LICENCE NUMBERS. Prempak-C 0 625mg PL0011/0161 Prempak-C 1 25mg PL0011/0162

BASIC NHS PRICE: £3 98 - 28 days For full prescribing information please refer to data sheet

REFERENCES 1 Dupont W D and Page D L (1991) Arch Int Med 151, 67-72 2 Lindsay R et al (1984) Obstet Gynecol. 63, 759-763 3 Kiel D P. et al (1987) NEJM, 317, 1169-1174 4 Ross R K et al (1989) Lancet, 1, 505 5 Stampfer M J and Colditz G A (1991) Prev Med, 20, 47-63 6 Stampfer M J et al (1991) NEJM, 325, 756-762 7 MIMs February 1992

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PREMARIN*
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

PREMPAK-C*
(Conjugated Oestrogens + Norgestrel)

P 25,395

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Altman, D. G., Gore, S. M., Gardner. M. J & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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Hytten F. E & Leitch I. (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26.

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April 1992, Vol. 99, pp. 275–282

COMMENTARIES

Fetal growth and adult disease

Recent findings suggest that ischaemic heart disease and stroke, and the associated conditions hypertension and non-insulin dependent diabetes, originate through impaired growth and development during fetal life and infancy. These diseases and certain others, including obstructive lung disease, may be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period of early life results in long term changes in physiology or metabolism (Lucas 1991). Animal experiments provide many examples of programming. For example, the insulin response to glucose is permanently impaired if rats are weaned onto a low protein diet for only 3 weeks (Swenne *et al.* 1987). This is likely to reflect persisting damage to the pancreatic β cells, which develop during late fetal life and infancy. Programming occurs because organs and systems mature during periods of rapid growth in fetal life and infancy. There are critical windows of time during which maturation must be achieved; and failure of maturation is to some extent irrecoverable. Nutritional deprivation in early life can programme the size and DNA content of many organs and systems. Which is affected depends on the precise time at which undernutrition occurs (Winick & Noble 1966).

Suspicion that programming plays a major role in the development of cardiovascular disease arose from a series of geographical studies in England and Wales. These showed that the large differences in cardiovascular mortality (deaths from ischaemic heart disease and stroke) between different areas of the country are paralleled by similar differences in neonatal mortality around 70 years ago (Barker & Osmond 1986). In those days high neonatal mortality in a population indicated a high incidence of low birthweight and poor maternal nutrition. The programming hypothesis is now being systematically explored by studying adults in middle and old age whose birth measurements and infant growth were recorded. From 1911 onwards every baby born in the county of Hertfordshire was weighed at birth, visited periodically by a health visitor throughout the first year, and weighed again at one year of age. Records of these visits have survived so that it is possible to trace men and women born 60 and more years ago and to relate these measurements to the later occurrence of illness and death and to the levels of known risk factors for cardiovascular disease. Similar long term follow-up studies are being carried out in Preston and a number of other places in Britain where in the past maternity hospitals made unusually detailed measurements on all newborn babies.

The first study in Hertfordshire was of 5600 men born in the eastern part of the county between 1911 and 1930. Among men who weighed 18 lb (8·2 kg) or less at one year of age, death rates from ischaemic heart disease were almost three times greater than among those who weighed 27 lb (12·3 kg) or more (Barker *et al.* 1989). Death rates fell progressively with increasing weight at one year. There were similar, though less strong, trends with birthweight. Death rates from stroke showed similar associations.

Examination of samples of men and women still living in Hertfordshire and Preston has shown that birthweight and infant weight are associated with adult blood pressure, glucose tolerance, plasma concentrations of fibrinogen, factor VII and apolipoprotein B, and with a tendency to store fat abdominally rather than peripherally (Barker 1992). These associations parallel those with death rates from cardiovascular disease in that higher early weight is associated with lower levels of each risk factor. The associations are remarkably strong and graded. For example, the percentage of men with impaired glucose tolerance, or non-insulin dependent diabetes, falls progressively from 40 among men with birthweights of 5·5 lb or less to 14 among those with birthweights of 9·5 lb or more (Hales *et al.* 1991). The associations between early growth and adult measurements are independent of social class, either at birth or currently, and of other confounding variables such as smoking.

A striking feature of these findings is that different risk factors are each related to different patterns of early growth. For example, blood pressure is related to birthweight but not independently to weight at one year, whereas plasma fibrinogen concentrations are strongly related to weight at one year but are unrelated to birthweight. This suggests that the critical period when blood pressure is sensitive to programming is during fetal life not infancy. Examination of birth measurements additional to weight identifies two groups of babies who develop high blood pressure as adults. One group, who also develop impaired glucose tolerance, have below average birthweight, head circumference and length, taking account of gestational age. Babies in this group would be recognized clinically as symmetrically growth retarded, the result of sub-optimal growth beginning in early pregnancy. An additional characteristic is that they have an above average ratio of placental weight to birthweight. A second group of babies who develop high blood pressure have above average birthweight, head circumference and placental weights/birthweight ratio, but below average length. These babies, who are not usually recognized clinically, have 'asymmetrical' growth retardation, thought to result from slowing of growth near term.

The relations between early growth and adult disease rates and levels of risk factors are continuous. They fall progressively up to the highest values of birthweight and weight at one year. If the criteria for successful fetal growth include adult health and longevity these findings reinforce the view that infants with significant intrauterine growth retardation need not necessarily be 'light-for-gestational age' (Altman & Hytten 1989). Intrauterine growth retardation seems to be widespread. It affects many babies whose birthweights are within the normal range, not just a few babies who are recognized clinically by their unusually small size and high risk of perinatal complications and death. We need to know more about the effects of intrauterine growth retardation on different organs and systems in the human fetus. For example, the paper by Hinchcliffe *et al.* in this issue of the Journal (p 296) has shown for the first time that asymmetrical retardation is associated with a substantial reduction in the number of nephrons, and that there is no post-natal compensation for this (Hinchcliffe *et al.* 1992).

Recent studies of 4-year old children in Salisbury, and 20-year-old men in Southampton, have shown similar associations between fetal growth, blood pressure and insulin response as were found in older people. We therefore know that these associations depend on influences which still affect fetal growth today: but we know little about what these influences may be. There are, however, clues. For example, a survey of 8600 pregnant women in Oxford showed that the highest ratio of placental weight to birthweight occurred in women who had the lowest haemoglobins and largest fall in mean cell volume during pregnancy (Godfrey *et al.* 1991). Research into the nutritional and other influences that modulate the growth of the fetus and permanently programme its metabolism is now a priority. It may hold the key to preventing cardiovascular disease and other important disorders in adult life.

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Retinoid therapy—a real hazard for the developing embryo

The Chief Medical Officer, Sir Donald Acheson, recently wrote to all United Kingdom physicians warning them of the potential dangers to pregnant women of excessive vitamin A consumption (Acheson & Poole 1990). He advised that liver and liver products such as pâté should be avoided in pregnancy because of concern that their high vitamin A content might represent a significant teratogenic risk to the developing embryo. Although the teratogenic effects of vitamin A have been well studied in animal models, there are only a score of reports of fetal malformation following vitamin A intoxication in humans (Acheson & Poole 1990). It seems timely, however, to remind obstetricians of the well-documented hazards of a class of drugs which closely resembles naturally occurring vitamin A, the synthetic retinoids.

It has been known for many years that vitamin A has an essential rôle to play not only in maintaining visual and reproductive function but also in regulating proliferation and differentiation of epithelial tissues. A deficiency of vitamin A results in hyperkeratosis of the skin and in squamous metaplasia of mucous membranes. Dermatologists recognised that it might therefore be beneficial in conditions characterized by excessive keratinization. In the 1960s high dose systemic vitamin A began to be investigated in a number of chronic hyperkeratinizing skin disorders. It was subsequently shown that a natural derivative of vitamin A, all-*trans*-retinoic acid, had a dramatic effect on certain disorders of keratinization (Schumacher & Stüttgen 1971) but its use had to be abandoned because of serious side effects.

In the late 1960s investigators working for Hoffmann-La-Roche Ltd in Basel, Switzerland, began to develop analogues of retinoic acid (retinoids) with more favourable therapeutic ratios than the natural vitamin in the hope that they would be more acceptable for clinical use (Bollag 1981). The two most promising of these compounds were made available to dermatologists for pilot studies in the mid 1970s. Reports rapidly appeared detailing the effects of these drugs on a wide variety of skin conditions.

Almost by chance it was discovered that one of them, isotretinoin (13-*cis*-retinoic acid: Ro-Accutane), was a potent inhibitor of sebaceous gland activity and thereby had an almost miraculous effect in patients with severe acne (Peck *et al.* 1979). Etretinate (Tigason), the other retinoid under study, was shown not only to be a potent inhibitor of abnormal keratinization but also to have a rapid and profound effect on the cutaneous immune response (Langner *et al.* 1984), explaining its ability to switch off pustule formation in generalized pustular psoriasis within a matter of 2-3 days (Fritsch 1984).

By the early 1980s it was apparent that the synthetic retinoids represented a major advance in the therapy of skin disease. Isotretinoin has revolutionized the management of severe nodulocystic acne. Etretinate has transformed the lives of many individuals with rare hereditary skin diseases (e.g., lamellar ichthyosis and Darier's disease) and is of major importance in the treatment of severe psoriasis (Hazell & Marks 1984).

Although these new vitamin A analogues appeared to be much better tolerated than retinoic acid (Bollag 1981), unfortunately it did not prove possible to dissociate their beneficial therapeutic effects from side effects characteristic of hypervitaminosis A. Both drugs caused unpleasant if not life-threatening changes in skin, hair and mucous membranes. They also adversely affected circulating lipid levels and at high dosage could induce abnormal new bone formation. Furthermore, animal studies suggested that they were no less teratogenic than equivalent doses of vitamin A (Hummler & Schüpbach 1981).

Following the thalidomide tragedy, no pharmaceutical company had been in the position of actively promoting a drug suspected to be a potent teratogen for use in essentially healthy women. The main indication for isotretinoin is severe nodulocystic acne, in which a short course of treatment can be expected to induce prolonged or permanent remission (Peck *et al.* 1979). Many of the potential beneficiaries of isotretinoin therapy are thus teenage girls or young women. When it was first released into the American market in 1982, clear warnings about the hazards of pregnancy during and for one month after therapy were given to prescribers, yet within 4 years 48 cases of congenital malformation associated with its use in early pregnancy had been reported to the US Food and Drugs Administration (Stern 1989). By mid 1991 a worldwide total of 105 cases had been reported to Hoffmann-La-Roche Ltd (Roche Products Ltd, UK, personal communication). This number should be contrasted with the several million patients to date who have received treatment with isotretinoin.

Unlike isotretinoin, which is rapidly eliminated from the body, etretinate is highly lipophilic and is readily taken up into adipose tissue from where it is only very slowly released. Its terminal elimination half-life is 120 days or more (Massarella *et al.* 1985) and traces of the drug can be found for up to 3 years after treatment has been stopped (DiGiovanna *et al.* 1989). The main indications for etretinate are rare genodermatoses or difficult psoriasis for which repeated or prolonged courses of the drug may be required. There was thus good reason to be circumspect about using etretinate in women of child-bearing potential and in most countries in Europe etretinate prescribing was restricted when it was introduced in 1982. In Britain, for instance, it was made available only to hospital pharmacies, effectively limiting its use to the nation's 250 dermatologists. By early 1991, Hoffmann-La-Roche Ltd had, nevertheless, received reports on more than 80 women exposed to etretinate during pregnancy and over 100 who conceived within 2 years of stopping therapy (Roche Products Ltd, UK, personal communication); elective termination was performed in many cases but in those pregnancies which were completed, fetal malformation was common (5 of 26 and 8 of 68 cases respectively). Because of undoubted under-reporting of pregnancies with normal outcomes and the inclusion of fetal abnormalities unlikely to be due to retinoid effect, the risk attributable to etretinate may be somewhat lower than these figures suggest.

Although both isotretinoin and etretinate are potent teratogens (and comparable in this respect to thalidomide) our knowledge of retinoid teratogenicity comes principally from isotretinoin use in America. It has been estimated that miscarriage occurs in 40% of pregnancies where the woman has taken isotretinoin in the first trimester and that in those pregnancies reaching 20 or more weeks gestation there is a 1 in 4 risk of major malformation (Lammer *et al.* 1988). Even brief exposure may be hazardous, as typical abnormalities have been reported in a child born to a mother who received isotretinoin for fewer than 4 days at one month of pregnancy (Hersh *et al.* 1985).

The pattern of malformation seen with the retinoids resembles experimental vitamin A teratogenicity. First trimester exposure to isotretinoin may affect four organ systems primarily: the brain, the craniofacies, the heart and major arteries, and the thymus (Lammer 1989). Absent or low-set, hypoplastic ears, maldevelopment of the facial bones, cleft palate, major congenital heart defects, thymic aplasia and hydrocephalus are characteristic. These defects suggest that isotretinoin interferes with normal neural-crest cell migration. In the few cases attributed to etretinate, abnormalities of the craniofacies and of limb development including meningoencephalocoele, multiple synostoses and absence of terminal phalanges have been seen (Sulik & Alles 1991).

As a result of the problems encountered after the launch of the retinoids, procedures for prescribing these drugs to women of child-bearing potential are now much stricter and include the following: (i) Pregnancy should be excluded by a negative pregnancy test within 2 weeks before starting therapy. (ii) Therapy is started only on the second or third day of the next menstrual period. (iii) Effective contraception must be practised for at least 4 weeks before, during and at least 4 weeks after treatment in the case of isotretinoin or 2 years in the case of etretinate. (In the United States, however, current recommendations are that pregnancy should be avoided 'for an indefinite period of time' after etretinate therapy.) (iv) Patients should be advised that any pregnancy occurring during treatment or in the post-treatment washout period must be reported immediately to the prescriber and that termination of the pregnancy may be advised on the grounds that there would be a substantial risk that the child, if born, would be seriously handicapped.

In order to ensure that patients fully understand the implications of treatment, specially designed consent forms should be signed before instituting therapy.

The search for safer retinoid drugs continues. Acitretin, a drug of comparable efficacy but much more rapidly excreted than etretinate, looked promising until it was found that a few patients seemed able to convert it to etretinate (Wiegand & Jensen 1991). There is some evidence from animal studies that not all biologically active retinoids are teratogenic (Teelmann 1989). For the present, however, women with severe skin disease will continue to be treated with these powerful teratogens and all doctors involved with family planning or childbirth should be aware of their significance.

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British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 278–280

The prevention of preterm delivery—can we afford to continue to ignore the cervix?

Preterm birth remains the major factor contributing to perinatal mortality and morbidity (Liston & Patel 1986). Preterm delivery occurs in approximately 6–8% of all pregnancies and is responsible for 75% of all perinatal deaths (Fuchs 1976). In addition, 85% of all neonatal deaths not attributable to anomaly are associated with preterm delivery (Rush *et al.* 1976), and 10% of the survivors of preterm birth suffer some form of handicap (Hull 1977).

Though preterm delivery may be iatrogenic, resulting from the management of a pregnancy-related problem, a significant proportion result from the spontaneous onset of labour before 37 completed weeks gestation. Fedrick & Anderson (1976) considering data from the first British perinatal mortality survey reported an incidence of spontaneous preterm labour of 16·7/1000, and in an analysis of 400 preterm deliveries, Rush *et al* (1976) found that 38% of all preterm deliveries resulted from spontaneous onset of labour.

The most overt symptom and sign of preterm labour is the presence of myometrial activity or uterine contractions. It is understandable, therefore, for the medical profession to have concentrated their attention on the manipulation of myometrial activity in its attempts to reduce the occurrence of preterm labour and its attendant morbidity. However, results have been disappointing. Tocolytics have been shown to have an effect, but they will only delay the progress of labour rather than prevent it (King *et al.* 1988).

Certain paradoxes surround preterm labour. It has been stated that preterm labour is always associated with uterine contractions (Turnbull 1957). However, at least 50% of women in apparently established preterm labour will have spontaneous cessation of contractions and will continue their pregnancy (Anderson 1981). All labouring women have contractions, but not all women with contractions are labouring. Conversely, it is not uncommon for women to approach preterm delivery with little appreciation of uterine activity (Pearce 1986). A common presentation of preterm labour is a history of vague abdominal discomfort, which may be attributed to a minor gastrointestinal disturbance by the pregnant woman only to find on admission that labour is well advanced. It is not uncommon for women to be admitted in the second stage of labour with the first indication of the imminent delivery being pelvic pressure and a desire to bear down. These observations suggest that a simple association between myometrial activity and progress in preterm labour cannot be made.

Though much attention has been paid to the physiology and function of myometrium, it is the cervix which has the dominant role for the majority of pregnancy. The cervix must remain as a firm tubular structure to retain the conceptus, and its tightly wound, circumferentially arranged collagen fibres are ideally suited to this purpose. However, within the relatively short timescale of labour the cervix changes sufficiently to allow the passage of the fetus without sustaining any permanent damage which could impair its function in any future pregnancy. Furthermore, within a few days of parturition the cervix has returned to its former state and function.

The appreciation of uterine activity, depends upon the development of tension within the wall of the uterus due to muscle contraction. However, in addition to muscle, the uterine wall contains 'elastic' elements (Coren & Csapo 1963). Little attention has been paid to the effects of these 'passive' elements on the function of the myometrium and the development of wall tension. The collagenous cervix makes up part of the uterine wall. Its compliance will down-modulate the tension developed by the myometrium, such that the greater its compliance the less the tension and the weaker the perceived contraction. The converse will also be true, the non-compliant cervix failing to modulate increases in uterine wall tension resulting in a rapid rise in intrauterine pressure and higher peak pressures. These effects and their influence on the intrauterine pressure waveform have been elucidated (Gee, 1986; Gee *et al.* 1988). Theoretically, with an infinitely compliant cervix, the first stage of labour would proceed infinitely quickly and there would be no wall tension, no intrauterine pressure and no perception of contractions! If resistance to delivery of the fetus is artificially removed, wall tension is reduced to zero, pressure is released and delivery is immediate i.e., a caesarean section.

This assessment goes a large way to explaining some of the clinical paradoxes surrounding preterm labour. Regarding current therapies for tocolysis, three groups could be hypothesized. In the first group, the women will present with an active myometrium but a non-compliant cervix. In such cases, high pressures will be generated within the uterus as a result of relatively mild myometrial activity (e.g., Braxton-Hicks contractions). As long as there is no change in the properties of the cervix, delivery is unlikely to occur. No treatment, or a placebo would appear to be equally effective. In the second group, the women will release prostaglandins and possibly other, as yet unknown agents, in response to uterine activity (Sharma *et al* 1973). Eventually these agents may affect cervical compliance and timely intervention to prevent such changes would be of benefit. This group will have a true response to tocolytic therapy. In the third group, where the cervix has undergone an increase in compliance (clinically apparent as cervical 'softening' or 'ripening'), depending on the degree, even the wall tension due to resting tone may be enough to produce gradual effacement and dilatation. Delivery would be inevitable. Thus for beta-sympathomimetics to have a demonstrable effect, the second group would have to be relatively large otherwise the benefits would be offset by their lack of effect in the other two groups. Presumably this is not the case. Indomethacin has also been used as a tocolytic agent in preterm labour. Unlike beta-sympathomimetics, the anti-prostaglandin action should affect both myometrial activity and cervical ripening, but results have not been promising (Keirse *et al.* 1989). Presumably, since the ripening effect is likely to antedate the contractions (the sequence observed in normal labour), the administration of this agent during preterm labour is likely to be after the event. Alternatively, the concentrations of the drug in the cervical tissues resulting from systemic administration may be inadequate to produce an effect.

We have become accustomed to manipulating cervical state for the purposes of promoting delivery, but even these mechanisms are poorly understood. Preterm cervical ripening has been described as an important cervical dysfunction (Uldbjerg 1989). Perhaps more research on cervical chemistry, pharmacology and their relation to the physical properties of the cervix to produce ripening should be promoted so that inhibition of this process could be tackled in a logical way. Work has been conducted on the chemical and physical changes which take place during ripening (Kleissl *et al.* 1978; von Maillot *et al.* 1979; Danforth *et al.* 1974), but the exact mechanism of action of ripening agents (e.g., prostaglandins, oestrogens, relaxin) are elusive. By understanding their action, a means of inhibition may be forthcoming.

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British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 280–282

Measuring gestational age: an uncertain proposition

Estimating the duration of pregnancy is fundamental for the clinical management of the pregnancy. Decisions whether to intervene in a post-term pregnancy or to deliver a woman preterm because of concern over maternal or fetal health require fairly precise estimates of gestational age. The interpretation of alpha-fetoprotein (AFP) levels also requires accurate estimates of pregnancy duration. In addition, there is often a need for the purposes of research and, occasionally, litigation to know, with precision, when a pregnancy began so that the role of a potential teratogen may be properly assessed.

Despite its fundamental importance to obstetric practice, there is still uncertainty over how best to measure gestational age during pregnancy. In the past decade, considerable interest has focused on the use of ultrasonography (Haddock 1986). Biparietal diameter measures can estimate gestational age within 1·2 weeks if the examination occurs before 18 weeks, but becomes very imprecise at older gestational ages. Head circumference, abdominal circumference, and femur length have been used without improving this variability. When two measurements are used together, a 20% reduction in this variability may be achieved (Jacobson 1991). Except for very early ultrasound assessments, this technology may not provide superior results to those obtained using Naegele's rule when the date of last menstrual period (LMP) is reliable. Moreover, in many parts of the world, ultrasonography is neither available nor necessarily of high priority.

Naegele's rule (subtract 3 months from the first day of LMP and add 7 days) is the most frequently used method for calculating the expected date of delivery. The method is trivially easy and requires no special tests. It is, however, subject to several sources of error. Inaccuracy of the woman's recall of dates (Zador *et al.* 1980) may result in random error in the calculation of gestational age. Missed early miscarriage may result in a pregnancy being dated from an earlier menstrual period and result in an estimate of gestational age which is incorrectly long. Conversely, non-menstrual bleeding in the first trimester may be mistaken for a menstrual period and used as the date of LMP (Treolar *et al.* 1967) resulting in an incorrectly short estimate of gestation. In practice, there is often little that can be done to prevent these errors. In addition, many clinicians rely upon the wheels provided by pharmaceutical companies to calculate the estimated date of delivery. There is, however, considerable error and variability between wheels, even when provided by the same manufacturer (Bracken & Belanger 1989).

The error associated with Naegele's rule is considerable. Kramer *et al.* (1988) compared the gestational age calculated from the last normal menstrual period to that determined by early ultrasound measurements of biparietal diameter in 11 045 pregnancies. Only 12% of infants identified as post-term (>42 weeks gestation) by the LMP method were post-term using ultrasound dating. The corresponding positive predictive values were 22% for preterm and 95% for term infants. Thus, if the LMP method indicates a post-term gestation, there is an approximately 8 in 9 chance that it is term, and, if it indicates a preterm gestation, there is an approximately 4 in 5 chance that it is term. LMP estimates that are outside of the term range (37–42 weeks) should always be considered suspect.

The reasons discussed above for why the LMP method is subject to error do not hinge on the validity of the method *per se*. There are, however, other sources of error which result from the assumptions on which the method is based. LMP-based gestational age is not equivalent to conceptional age (age measured from time of conception) and is, on average, 2 weeks longer. Thus, while we think of the 'normal' pregnancy as lasting 40 weeks, the true length is really 38 weeks. As reviewed by Saito *et al.* 1972, two studies of pregnancies dated from conception reported the average gestation to last 267 and 269 days with a standard deviation of 7·6. Thus, only 5% or 6% of pregnancies should be post-term, yet studies often report post-term rates of 10% or more based on Naegele's rule (Grennert *et al.* 1978; Berg *et al.* 1990). The validity of the LMP method rests on two assumptions, first, that each woman's cycle is an invariant 28 days long, and, second, that ovulation (and hence fertilization) always occurs at midcycle. While these assumptions are, on average, correct, there is considerable variability between and within women. For example, Chiazze *et al.* (1968) studied 30 655 cycles in 2316 women. The mean cycle length was 29 days (SD 7·5, mode 27, range <7 to >50). Younger women had slightly longer and more variable cycles.

Dating from conception would be optimal. Two studies compared LMP estimates of gestational age to those based upon basal body temperature (BBT) taken to determine date of ovulation, and approximately conception. Saito *et al.* (1972) found that 15·5% of women were delivered post-term according to LMP dating, while only 4·5% were post-term according to BBT dating. This difference was almost entirely due to women with 'delayed' ovulation and long cycles. In a similar study of 317 women attending a family planning centre (Boyce *et al.* 1976), 70% of births classified as post-term based on LMP dating were within the term range if gestation was calculated using BBT to estimate date of conception. The LMP age exceeded the 'true gestational age' calculated from BBT by an average of 12 days (after correcting for the average 2-week difference between 'conceptional' and 'gestational' age). In those pregnancies classified as post-term, the LMP estimate of gestational age was greater than the true age by 1 week in 70% and greater by 2 weeks in 30%. There was also a small number of gestations that were identified as term by the LMP method and as post-term using BBT dating.

Information about day of ovulation is rarely available. There have been attempts to predict ovulation from the menstrual cycle length alone. Based upon physiological experiments in humans, Knauss concluded that, despite variation in the pre-ovulatory (follicular) phase of the menstrual cycle, the post-ovulatory (luteal) phase was a constant 14 days long (Hartman 1962). Ogino reached a similar, although not as rigid, estimate. This became incorporated into the family planning literature as the 'Ogino-Knauss' rule, the basis for the rhythm method of contraception. As demonstrated in several studies, the rigidity of this estimate is unjustified as there is significant variation in the luteal stage of the cycle (Flushman 1957; Matsumoto *et al.* 1962; Vollman 1966).

A recent analysis of 5688 mothers and their infants found a striking trend between reported menstrual cycle length and the proportion of infants classified post-term (>42 weeks) and post-date (>40 weeks) using Naegele's rule (Berg 1991). In women with cycles that were only 14–20 days long, there were no post-term infants and only 21% were post-date. By comparison, women in the longest cycle length category (36 to 42 days) had 14·6% post-term and 53·7% post-date deliveries. When the Ogino-Knauss method was used to calculate gestational age correcting for cycle length (days since LMP–(cycle length–28)), instead of these trends being eliminated, they were reversed, suggesting the method over-corrects for cycle length. This is consistent with the frequent observation that the rhythm method of birth control is less than 100% effective. A full one-third of the women in this study had cycles that were longer than 28 days, and, for this analysis, the women were already pre-selected for having regular cycles <43 days long. Thus, this issue affects more than an insignificant minority of women.

Accurate dating of pregnancy is desirable, both from the clinician's perspective as well as from that of the expectant mother. Yet, Naegele's rule often errs by a clinically significant degree resulting in an incorrect diagnosis of post-term gestation. Does this mean all pregnancies should be dated using early ultrasound as suggested by at least one group (Kramer *et al.* 1988)? While this may be appropriate where technological resources are available, it might be of questionable benefit when they are limited. Information, if reliable, about menstrual cycle length may help somewhat to determine pregnancy duration, especially if a post-term gestation is suspected. By this point in pregnancy, ultrasound dating is no longer highly accurate for determining gestational age anyway. While a blanket policy of early ultrasound dating may not be warranted, it may be useful to target women with long or irregular cycles for this procedure.

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British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp 283–286

OBSTETRICS

Home visits for pregnancy complications and management of antenatal care: an overview of three randomized controlled trials

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ABSTRACT

Objective To examine whether a policy of home visits reduces the amount of antenatal care provided by hospital maternity units.
Design A meta-analysis of three randomized controlled trials.
Setting 9 maternity units in France.
Subjects 1410 women with pregnancy complications.
Intervention 1 or 2 home visits a week by a midwife.
Main outcome measures Admission rate and length of stay in hospital.
Results The home-visiting system did not affect the hospital admission rate (typical odds ratio = 0·9; 95% CI = 0·7–1·2). In each trial, the length of hospital stay did not differ between the intervention and the control groups.
Conclusions The home-visiting system did not greatly alter the practice of antenatal hospital admission in the maternity units studied. The results question the way the health services were used and suggest that a better integration of hospital and home services is needed to make a more rational use of health care resources.

A home-visiting system is provided during pregnancy in several European countries (Blondel *et al.* 1985). It is usually intended to give appropriate care, health advice and social support to high risk women. In France, in some areas, priority is given to women in poor social circumstances and midwives aim to act as an intermediary between the family and the health services. In other areas close to the main public hospitals, domiciliary midwives provide clinical care for women who have pregnancy complications, with the aim of avoiding hospital admission or numerous visits to the outpatient clinic.

To establish whether a home visiting system results in the appropriate use of health services, we conducted an overview of the randomized controlled trials in which home visits were prescribed for pregnancy complications, and we assessed the effect of this type of care on the antenatal admissions and the number of visits.

Method

We selected trials in which home visits were prescribed for pregnancy complications, and clinical care was the main task of the domiciliary midwives. Two published trials (Spira *et al.* 1981; Blondel *et al.* 1990) and one unpublished (G. Mellier *et al.* unpublished observations) were identified through the Oxford Database of Perinatal Trials (Chalmers *et al.* 1986) or by personal contacts (Table 1). Unpublished information within these three trials was used particularly in order to have homogeneous definitions of the criteria.

The first trial (Spira *et al.* 1981) was conducted in Seine-Saint-Denis, a suburb of Paris, in 1978–80, 2 years after the introduction of the home-visiting system. The other two were carried out later, one in Lyon (G. Mellier, personal communication), the other in Paris (Blondel *et al.*, 1990). Several maternity units participated in the Seine-Saint-Denis and Paris trials, both in private and public hospitals, and the Lyon trial was conducted in a single teaching hospital. Women were identified either at a visit to the outpatient clinic or at proposed discharge. The entry criterion in all three trials was a pregnancy complication. In the Paris trial women were eligible if they had threatened preterm labour. This was the main indication in the Seine-Saint-Denis trial (70% of the women) and the Lyon trial (57% of the women); most of the other women were included in these two latter trials because of pregnancy-induced hypertension. In addition, the Paris trial was restricted to women who spoke French fluently because they had to answer a self-administered questionnaire about satisfaction with medical care.

In each trial women were allocated to the intervention and control groups by randomization. In the Seine-Saint-Denis and Paris trials, sealed envelopes were used. In the Lyon trial the allocation was done from a list of random numbers by a person who did not know the patients. In the Seine-Saint-Denis trial 11% of the women were lost after randomization. The main

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Table 1. Protocol and sample size in the three trials

	Seine-Saint-Denis (Spira *et al.* 1981)	Lyon (Mellier unpublished)	Paris (Blondel *et al.* 1990)
Years	1978–80	1983–87	1985–87
Population	Hospital based	Hospital based	Hospital based
Entry criteria	Pregnancy complications	Pregnancy complications	Threatened preterm labour
Allocation to intervention	Random	Random stratified by complication	Random stratified: inpatient ward/outpatient clinic
No. of women randomized (Intervention/control)	501/495	196/196	79/79
No of women in analysis	458/425	188/187	79/73
Mean weeks of gestation at study entry (Intervention/control)	27·9/28·5	27·4/28·0	31·0/31·0

reasons were moving to another area (18 women in the intervention group and 25 in the control group) and no antenatal care after study entry (14 and 25 women respectively). In the Paris trial five women were missing in the control group because their medical records were lost. In the Lyon trial the proportion of women excluded after enrolment was 6% and was similar in the two study groups. These women were living far from the hospital or did not speak French. The review involved a total of 725 women in the intervention group and 685 women in the control group. Comparability between the intervention and control groups at study entry was assessed in the three trials. The two groups were not significantly different with regard to social environment, age, parity, obstetric history, and gestational age at study entry. Nevertheless, in the Lyon trial 8·6% of women in the intervention group had a previous small-for-gestational age (SGA) baby compared with 1·6% in the control group.

In the three trials, the control group received the usual care provided by the maternity units, with visits to the outpatient clinics and hospital admission if thought necessary. The intervention group received one or two home visits a week by midwives in addition to the usual care.

We used the following indices of outcome: number of antenatal visits to outpatient clinic; hospital admissions and length of stay in hospital. Quantitative analysis of the results regarding hospital admission (typical odds ratio and its confidence interval) used a method described by Yusuf *et al.* (1985).

Results

The average number of home visits varied between the three trials, from 4·6 to 6·5 (Table 2). The average number of visits to the outpatient clinic after study entry was significantly lower in the intervention group than in the control group in the Lyon and Paris trials. In the Seine-Saint-Denis trial, these data were not recorded but the overall number of antenatal visits was slightly lower in the intervention group. In each trial, the rate of admission and the mean stay in hospital did not differ significantly between the two groups. In the Lyon trial, separate analyses were conducted for each complication. In the group who had threatened preterm labour, 20·6% of women in the intervention group and 19·2% of women in the control group were admitted to hospital at least once ($P>0{\cdot}05$). In the group enrolled because of hypertension the proportions were 33·3% and 34·4% respectively ($P>0.05$).

The pooled data from the three trials showed that the typical odds ratio for admission rates was 0·9 (95% CI 0·7 to 1·2) (Table 3).

Discussion

No difference was observed in the admission rates between the two groups in the pooled data from these three studies. This result cannot be explained by a longer delay between study entry and delivery in the intervention group as in all three trials, gestational age at study entry and the preterm delivery rate did

Table 2. Medical care after study entry in the three trials

	Seine-Saint-Denis			Lyon			Paris		
	Intervention		Control	Intervention		Control	Intervention		Control
Mean number of home visits	6·5			5·1			4·6		
Mean number of visits to outpatient clinic	8·8*	$P\geqslant 0{\cdot}05$	9·3*	3·0	$P<0{\cdot}05$	3·8	3·0	$P=0{\cdot}01$	4·0
Percentage of women admitted to hospital	22·4	$P\geqslant 0{\cdot}05$	26·9	25·5	$P\geqslant 0{\cdot}05$	25·1	45·6	$P\geqslant 0{\cdot}05$	35·6
Mean length of stay of women admitted (days)	1·9†	$P\geqslant 0{\cdot}05$	1·8†	9·9	$P\geqslant 0{\cdot}05$	7·5	9·4	$P\geqslant 0{\cdot}05$	8·3

*Total number of visits during pregnancy.
†Weeks.

Table 3. Effect of home visits on hospital admission rates in the three trials

Trial	Intervention	Control	Odds ratio (95% CI)
Seine-Saint-Denis	102/456	114/424	0·8 (0·6–1·1)
Lyon	48/188	47/187	1·0 (0·6–1·6)
Paris	36/79	26/73	1·5 (0·8–2·9)
Typical odds ratio			0·9 (0·7–1·2)

not differ significantly between the intervention and the control groups. The lack of difference between the admission rates is unlikely to stem from a higher rate of severe complications in the intervention group than in the control. Risk factors were similar in both groups in the Seine-Saint-Denis and Paris trials. In the Lyon trial more women in the intervention group had had a SGA baby, but the small number of women affected could not have greatly influenced the overall admission rates.

The results of several other randomized controlled trials have provided no evidence that home visiting systems had a beneficial effect on low birthweight or preterm delivery, either when social support was provided for high risk women throughout pregnancy (Elbourne *et al.* 1989; Bryce *et al.* 1991), or when home visits were made to women with pregnancy complications (Spira *et al.* 1981). For example, Spira *et al.* (1981) found preterm delivery rates of 10·1% in women who had home visits and 7·3% in those who had standard care, corresponding proportions of low-birthweight babies (<2500 g) were 11·1% and 9·5%. In this situation, other benefits should be considered, such as the rational use of health services, in particular by the reduction of antenatal visits and hospital admissions.

The effect of domiciliary care on hospital admissions varies according to the aim of the care provided. Oakley *et al.* (1990) found that a system of home visits by midwives to women who had had a low birthweight baby, intended to give them social support throughout pregnancy, reduced the hospital admission rate. Several other studies have assessed the efficacy of domiciliary surveillance incorporating uterine activity monitoring and nursing (Morrisson *et al.* 1987; Iams *et al.* 1988; Hill *et al.* 1990). These showed that this kind of care had no effect on hospital admission rates for preterm labour. This lack of difference may be explained by the fact that monitoring was implemented in the second or the third trimester of pregnancy with the specific aim of early diagnosis of threatened preterm labour. This assumed that efficient home monitoring would diagnose a large number of threatened preterm labours, and that a high rate of hospital admission would give the women the appropriate treatment in time. In contrast, when home care is provided for women who would otherwise be admitted to hospital, this type of care has a great effect on admissions, Dawson *et al.* (1989) found that domicilliary surveillance incorporating telephonic fetal heart rate monitoring avoided hospital admissions in more than half of the study sample. There is no such evidence when domiciliary surveillance is not an alternative to inpatient care.

In France, therefore, the main objective of home care for women with complications, namely to avoid hospital admissions, was not achieved in the three randomized trials included in our study. There may be several reasons. If home visits are added to usual care, complications are more likely to be detected and may result in more frequent hospital admissions. Women with domiciliary care may also be more aware of the signs of pregnancy complication and go to hospital in an emergency more frequently. The beneficial effect may be an early detection of pregnancy complications or of the recurrence of complications. Thus in a study of home uterine activity monitoring, preterm labour was diagnosed earlier in the monitored group than in the other group, and this could explain the lower preterm delivery rate in the monitored women than in the others (Morrisson *et al.* 1987). Nevertheless, our overview suggests that hospital admissions were sometimes unnecessary since pregnancy outcome did not differ significantly between the home care group and the control group in the three trials.

The potential benefits of home visits for women themselves should also be considered. In the Paris trial 78% of the women who had home visits were very satisfied with their antenatal care compared with only 44% in the other group (Blondel *et al.* 1990). In this study 89% of the women who had home care considered that it was the best antenatal care arrangement when threatened preterm labour was diagnosed. Furthermore we found that women cared for at home received better support than the women who had no home visit. They were more likely to have a family worker to provide help with domestic work and child care at home (Spira *et al.* 1981). Women who had home care were also more likely to receive extra help from family members or other persons, when threatened preterm labour was diagnosed, than women in the other group. Women who already had children were particularly likely to receive this help (Blondel *et al.* 1991).

We conclude that home care by domiciliary midwives did not lead to a decrease in hospital admission rates but it could be a very appropriate system of care for women with complications as it seems to meet their needs. Nevertheless, as the cost of care is very high, a better integration of hospital and home care services should be considered in order to reduce hospital admissions for women cared for at home. For example the domiciliary midwives might be on call in case of emergency at least during daytime and see the women at home if necessary. Moreover, some guidelines concerning the hospital admission of women with home care might be defined by the hospital medical staffs with the domiciliary midwives. The objective would be then to maintain the home visiting system and guarantee a rational use of health services.

Acknowledgments

We are grateful to Professor Georges Mellier for making unpublished data available for this review, to Nadine Spira for giving details about the Seine-Saint-Denis trial and to Monique Kaminski for helpful comments.

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Received 23 April 1991
Accepted 25 November 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 287–291

OBSTETRICS

Gammaglutamyltransferase, aspartate and alanine aminotransferases and their ratio, mean cell volume and urinary dolichol in pregnant alcohol abusers

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ABSTRACT

Objective To study the activities of serum gammaglutamyltransferase (GGT), aspartate and alanine aminotransferases (AST, ALT), and their ratio (AST/ALT), mean erythrocyte cell volume (MCV) and urinary dolichol output in alcohol-abusing pregnant women, and compare the results to those of abstinent pregnant women.
Design Prospective descriptive study.
Setting Special outpatient clinic for pregnant problem-drinkers in the department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Finland.
Subjects 25 pregnant women referred to the special clinic at between 12 and 24 weeks gestation, they consumed at least 150 g of ethanol weekly, and a control group of 20 abstinent pregnant women matched for age, parity and smoking habits.
Interventions The women were encouraged to visit the clinic at 2–4 week intervals. At each visit blood and urine samples were obtained, and the women were interviewed on their alcohol consumption during the previous weeks and encouraged to abstain in the future.
Mean outcome measures Neonatal condition, fetal alcohol effects (FAE) in the newborn. Serum activities of GGT, AST and ALT, the AST/ALT ratio, the MCV, and the urinary concentration of dolichol in alcohol-abusing women with either healthy or FAE infants, compared with those of abstinent women with healthy infants.
Results Of the 25 alcohol-abusing women 13 gave birth to infants with FAE and 12 to healthy infants. All the women in the control group gave birth to healthy infants. GGT, AST and ALT activities were increased in all alcohol-abusing women, regardless whether the infant had FAE or not. GGT was the best of these markers, GGT activities above the 95th normal centile were found in 33% of the samples from all alcohol-abusing women. The AST/ALT ratio, MCV and urinary dolichol concentration were poor indicators of abusive drinking.
Conclusions Maternal alcohol abuse is difficult to assess by laboratory tests. Of the commonly used and easily available tests, GGT proved to be the best in our study.

Alcohol abuse during pregnancy can lead to the so called fetal alcohol syndrome or to the milder form of this syndrome 'fetal alcohol effects' (FAE) (Rosett 1980; Streissguth *et al.* 1980). Today, FAE is the most common of known prenatal causes of motor and mental developmental delay in children (Abel & Sokol 1986). Therefore, it is of great importance to detect alcohol abuse during pregnancy as early as possible so that counselling and treatment can be started. So far the most common laboratory tests used for this early detection have been serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gammaglutamyltransferase (GGT), or the ratio of AST to ALT. Another commonly used indicator of excessive drinking has been increased mean erythrocyte cell volume (MCV) (Skude & Wadstein 1977; Matloff *et al.* 1980). However, none of these tests has proved to be ideal in the detection of problem-drinking and, consequently, there has been a continuous effort to develop new, more sensitive and specific markers.

Three decades ago Pennock *et al.* (1960) discovered a group of long-chain polyisoprenoid alcohols, the dolichols, which were later found to be synthesized most abundantly in the kidney, spleen and liver (Elmberger & Engfeldt 1985; Elmberger *et al.* 1987). Dolichols are excreted into urine, and urinary dolichol output is increased in alcholic subjects (Pullarkat & Raguthu 1985). Urinary excretion of dolichols could therefore be a potential marker for alcohol abuse in pregnant women. The aim of the present study was to compare this new test with the traditional markers AST, ALT and their ratio, GGT, and MCV for the detection of pregnant alcohol abusers.

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Subjects and methods

Twenty-five women between 12 and 24 weeks gestation were referred by local midwives to a special outpatient clinic for pregnant problem-drinkers. This clinic was established in 1983 and has proved to be popular, the attitudes of the clinic are positive and encouraging to a pregnant alcoholic. After the counselling and a plea for abstinence, the drinkers were encouraged to visit the department at 2–4 week intervals for additional counselling and prenatal care. At each visit, the women were asked about their alcohol consumption during the previous weeks and encouraged to abstain in future. In addition to alcohol consumption of at least 150 g of ethanol weekly, three of the women smoked marijuana and used amphetamine and buprenorphine intravenously, and one of these women developed hepatitis B at 36 weeks gestation.

As controls we followed throughout pregnancy 20 abstinent women of the same age, parity and smoking habits. Our aim was to include 25 control women, but five of the control women had taken iron supplements during pregnancy and they were excluded from the study to avoid problems with the analysis of MCV.

None of the women in the analysis took iron or folic acid supplements. Their characteristics are detailed in Table 1.

The women attended the clinic between 0900 and 1100 hours when venous blood samples were obtained for analyses of AST, ALT, GGT and MCV. Routine laboratory methods were used. Urine samples for dolichol analysis were obtained at the same time, and kept frozen at −20°C until analysed by the method described previously (Turpeinen 1986; Roine *et al.* 1987a) but with a few minor modifications: 10 ml of urine sample at pH 5 was used instead of 20 ml, heneicosaprenol as an internal standard was replaed by dolichol-17 and to improve recovery, 90% methanol instead of 100% methanol was used for washing the C_{18} extraction columns. The dolichol concentrations obtained were related to urinary creatinine concentration determined by the kinetic picrate method (Bartels *et al.* 1972).

The statistical analyses were performed with ANOVA and Spearman's rank correlation test after the subjects had been divided into two groups based on whether the newborn was healthy or showed FAE. The 95th normal centiles for GGT, MCV, dolichol, AST, ALT and their ratio were calculated normally.

The results of blood and urine samples obtained during the acute phase of hepatitis were excluded from the analyses.

Results

All but five infants of the alcohol-abusing women were not distressed at birth and during the first week. Of the five infants one suffered from cerebral oedema and low blood glucose levels, three from severe symptoms of alcohol and drug addiction, and two of these had to be given intravenous morphine in decreasing doses, and one infant had clubfeet and congenital nephrosis on the left and renal cysts on the right. Thirteen of the infants of the alcohol-abusing women showed features of fetal alcohol effects (FAE) (Table 2). It is planned to follow as many as possible of these infants up to the age of 7 years and the results will be published at a future date in a paediatric thesis. All the infants of the abstinent women were healthy.

Neither MCV, the activities of AST, ALT or GGT, nor urinary excretion of dolichols increased with advancing gestational age. Therefore all the data for each of the variables collected during the whole pregnancy were grouped together. The mean activities of AST, ALT and GGT were highest in the women with FAE, but even the alcohol-abusing women with healthy infants had higher mean AST, ALT and GGT activities than the control women (Table 3). The mean ratio of AST/ALT did not differ significantly between the three groups. MCV was highest in alcohol-abusing women with healthy infants (Table 3).

All groups of pregnant women had a mean urinary dolichol excretion exceeding the upper normal limit in general population (Roine *et al.* 1989). Consequently, increased excretion of dolichols into urine was a poor marker of both alcohol abuse during pregnancy as well as development of FAE. Compared with non-alcoholic pregnant women, the excretion of dolichols into urine was increased only in 6% of the samples from the alcohol-abusing women and in 4% of samples from those who subsequently gave birth to an infant with FAE (Fig. 1). Thus the usefulness of increased urinary dolichol excretion in the detection of alcohol abuse in pregnant women was of same level as that of MCV (Fig. 1). In this study maternal serum GGT was the best indicator for alcohol abuse. GGT activities above the 25th centile were found in 33% of the samples from all alcohol-abusing women and in 52% of those who gave birth to infants with FAE (Fig. 1).

Table 1. The clinical characteristics of the pregnant women in the study

	Alcohol abusing-women with		
	FAE infants (*n* = 13)	Healthy infants (*n* = 12)	Controls (*n* = 20)
Maternal age (years)	28·7 (4·9)	28·8 (7·3)	27 6 (7·3)
Nulliparous	12	9	16
Smoking women	13	11	14
Gestational age at delivery (weeks)	39·7 (1·9)	40·6 (1·4)	40·0 (1·1)
Birthweight (g)	2708 (335)*	3451 (566)	3443 (362)
Placental weight (g)	475 (72)	591 (150)	572 (162)

*$P<0.01$ compared with the other two groups.
Results are mean (SD) values.
FAE = fetal alcohol effects.

Table 2. Characteristics of 13 infants with fetal alcohol effects

Infant no.	Birthweight (g)	Retarded growth*	Facial features†	Neurological aberrations‡	Malformations
1	2170	+	+	+	
2	2360	+	+	–	Clubfeet
3	2470	+	+	+	
4	2890	+	+	+	
5	2340	+	+	+	Cerebral oedema
6	2530	+	+	+	
7	2765	+	+	+	
8	2830	+	+	+	Clubfeet, renal anomalies, undescended testis
9	2960	–	+	+	
10	2790	+	+	+	
11	3080	+	+	+	
12	2640	+	+	–	
13	3380	–	+	+	Ventricular septal defect

*Birthweight < 10th normal centile and/or weight, length and head circumference < mean–2SD at follow up of 1 year.

†Broad nasal bridge with upturned head of nose, short palpebral fissures, hypoplastic philtrum and maxilla, thin upper lip, retrognathia.

‡Physical and/or mental developmental delay and/or hypotonia, irritability, and motor incoordination; infants nos. 1, 5 and 7 had pathological electroencephalograms 1–5 days after birth and infant no 9 had epileptic seizures.

The MCV, or activities of AST, ALT or GGT, or urinary excretion of dolichols did not correlate with maternal smoking or the infant birthweight or placental weight (data not shown).

Discussion

We compared established markers of chronic alcohol abuse—AST, ALT, their ratio, GGT and MCV to a new marker, increased urinary dolichol excretion, in alcohol abusing pregnant women. The half-life time of dolichol in urine is 3 days, and the excretion of dolichol in urine is increased both after chronic alcohol abuse and extremely heavy weekend drinking in non-pregnant subjects (Roine *et al.* 1987a, b). Furthermore, we also studied the relevance of these markers in women with excessive drinking leading to fetal damage, as 13 of the alcohol-abusing women gave birth to infants with FAE.

Although all the pregnant women had clearly increased mean urinary dolichol excretion compared with non-pregnant subjects (Roine *et al.* 1989), increased urinary excretion of dolichol proved to be of little value in the detection of alcohol abuse in the pregnant women. This can be explained by the fact that pregnancy, *per se*, leads to increased urinary dolichol excretion (Roine *et al.* 1989), and, consequently, the further increasing effect of alcohol abuse may be small. It is also possible that the alcohol consumption of the women in the present study was not heavy enough to increase the urinary excretion of dolichols. Periodic alcohol consumption of 420 g of ethanol of 10 days did not increase urinary dolichols in healthy men (Roine 1988), but when a similar amount was consumed during 2 days the excretion of urinary dolichols started to increase (Roine *et al.* 1987b). However, pregnancy becomes unlikely at consumption levels in this range (Van Thiel & Lester 1979). After cessation of excessive drinking, the urinary excretion of dolichols decreases to normal in 5 days of abstinence (Roine 1988). This may partly explain why urinary dolichol excretion was of little value in the detection of alcohol abuse in pregnant women. Although the urinary dolichol concentration in women who subsequently gave birth to an infant with FAE was not different from that in non-alcoholic pregnant women, the test could still be of value in the diagnosis of alcohol related disorders. Wisniewski *et al.* (1983) have reported elevated urinary dolichol levels in alcohol-exposed newborn infants.

Table 3. Enzyme activities, erythrocyte cell volume and dolichol excretion in the three study groups

	Alcohol abusing women with		
	FAE infants	Healthy infants	Controls
No. of samples	46	36	57
AST (IU/l)	24·5 (18·4)*	20·1 (14·0)*	13·2 (7·3)
ALT (IU/l)	27·0 (26·5)*	23·4 (26·2)*	14·1 (12·9)
AST/ALT ratio	1·2 (0·7)	0·9 (0·6)	1·1 (0·7)
GGT (U/l)	32·4 (28·4)*	18·5 (12·4)*	10·2 (6·8)
MCV (fl)	91·4 (4·4)	93·0 (4·0)*	90·9 (4·3)
Dolichol (μg/mmol creatinine)	22·0 (10·0)	25·4 (16·4)	23·2 (7·9)

Significance of difference compared with the control group *$P<0·05$.

Results are means (SD) values.

Abbrevations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gammaglutamyltransferase; MCV = mean erythrocyte cell volume, FAE = fetal alcohol effects.

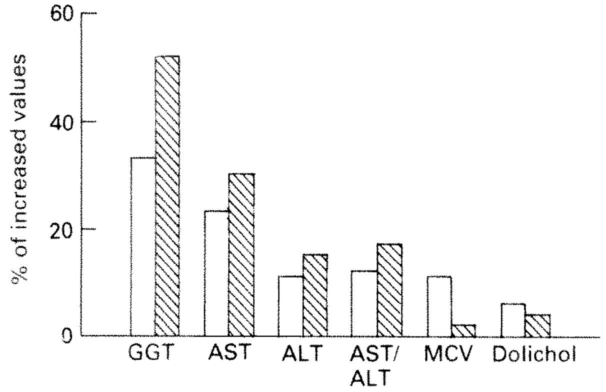

Fig. 1. The frequencies of high maternal serum activities (> the 95th normal centile) of gammaglutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), the AST/ALT ratio, mean erythrocyte cell volume (MCV) and increased urinary dolichol excretion in samples of all alcohol-abusing women (□) and those who gave birth to infants with fetal alcohol effects (▨)

The activities of AST and ALT rise in response to liver cell damage but are insensitive markers of alcohol abuse (Skude & Wadstein 1977; Editorial, *Lancet* 1980; Holt *et al.* 1981). We found high activities of AST and ALT in 23% and 11%, respectively, in our sample of alcohol abusing pregnant women. These figures agree with those found in non-pregnant alcohol abusers (Skude & Wadstein 1977; Editorial *Lancet* 1980; Holt *et al.* 1981) showing that AST and ALT activities are insensitive even if maternal alcohol abuse is severe enough to induce fetal damage.

In recent years the AST/ALT ratio has been used as an indicator of alcohol related liver disease, and a value of 1·5 is said to be indicative and a ratio over 2 highly suggestive of alcohol related liver damage (Cohen & Kaplan 1979; Spech & Liehr 1983). The elevated AST/ALT ratio in alcoholic liver disease is primarily due to the low ALT activity in patients with alcoholic liver disease (Matloff *et al.* 1980). This is at least in part a consequence of pyridoxal 5' -phosphate depletion (Diehl *et al.* 1984) which is common in alcoholics (Lumeng & Li 1974). The sensitivity of increased AST/ALT ratio as a marker of alcohol abuse has not been studied in pregnant women, and in our subjects with no evidence of serious liver damage its value was poor.

Although high GGT proved to be the best indicator of alcohol abuse in this study, it is not specific for alcohol. Pancreatic and heart diseases, old age, obesity, smoking, and all drugs inducing liver enzyme activity may lead to elevated serum GGT levels (Penn & Worthington 1983; Salaspuro 1986). Furthermore, the duration of alcoholism may have some effect on GGT levels, as individuals with a long history of alcohol abuse have higher GGT levels than those with shorter abuse (Horner *et al.* 1979). These factors may decrease the reliability of elevated GGT as a marker of alcohol abuse. On the other hand, correlation between alcohol abuse and GGT is known to be better in women than in men (Reyes *et al.* 1978; Garvin *et al.* 1981), and in our study e.g., maternal age and smoking habits were similar in all of the study groups. In view of our present and previous results and those of others (Barrison *et al.* 1982; Ylikorkala *et al.* 1987), GGT seems, at present, to be the best generally available marker of alcohol abuse during pregnancy.

Ethanol has a direct toxic effect on the red cells and, therefore, macrocytosis is common in alcoholics. In the present study MCV was highest in alcohol-abusing women with healthy infants, but in fact only 11% of alcohol-abusing women had elevated MCV values. The present data agree with two previous reports that MCV values are poor indicators of alcohol abuse in pregnancy (Barrison *et al.* 1982; Halliday *et al.* 1982). Poor nutritional balance and possible iron deficiency in pregnant alcoholics may partly compensate for the alcohol induced increase in MCV. Another explanation may be the female drinking habits, as women seldom drink continuously for 120 days, which is the period needed before the red cells swell (Wu *et al.* 1974; Chick *et al.* 1981). In addition, most of the women in our study were smokers, and smoking is known to increase MCV values (Wu *et al.* 1974; Chick *et al.* 1981). This probably is the explanation for the relatively high upper normal limit for MCV in our study, and can partly explain the poor sensitivity of the test in the detection of alcohol-abusing women.

In conclusion, maternal alcohol abuse is difficult to approach by laboratory tests. Of the commonly used tests, GGT proved to be the best in our study. Urinary dolichol excretion was—in contrast to nonpregnant population—far too insensitive in the detection of problem drinking among pregnant women.

Acknowledgment

The study was supported by the Jahnsson Foundation.

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Received 28 June 1991
Accepted 3 December 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 292–295

OBSTETRICS

Serum relaxin as a potential marker for preterm labour

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ABSTRACT

Objective To determine whether high serum relaxin concentrations in the 30th week of pregnancy were associated with preterm labour.

Design Case-control study.

Setting Two antenal clinics of the Department of Obstetrics and Gynecology University Hospital of Aarhus.

Subjects A cohort of 991 women (82% of 1203 eligible) in the 30th week of pregnancy attending one of the two antenatal clinics. The cases comprised 23 (2·4%) women without pre-eclampsia or small for gestational age babies, who were delivered spontaneously before 37 completed weeks gestation. The control group of 46 women was randomly selected from the rest of the cohort, all of them were delivered at term.

Interventions Blood samples were collected at 30 weeks gestation and stored for analysis.

Main outcome measures Serum relaxin concentrations estimated by ELISA technique, length of gestation at delivery.

Results The mean serum relaxin concentrations in the 30th week of pregnancy was 455 (SD 169) pg/ml and 327 (SD 139) pg/ml in the cases and controls, respectively (P = 0·003, *t* test). In women with preterm delivery a negative correlation was found between relaxin concentration in the 30th week of pregnancy and the gestational age at parturition (*r* = −0·53, *P* = 0·02).

Conclusion High relaxin concentrations may be associated with preterm delivery but the present results need confirmation in large scale studies.

Preterm delivery is associated with 85% of the early neonatal deaths when babies with congenital deformations are not included (Rush *et al.* 1976). Consequently, the prevention of this condition is one of the most important challenges in the modern obstetrics. Preterm delivery is more likely if the woman has the following characteristics; poor socio-economic status, strenuous working conditions, vaginal bleeding during the pregnancy or a ripe cervix early in the third trimester. However, most preterm labours remain unexplained and the rate of preterm delivery remains unchanged at about 5% (Kramer 1987). Difficulty in identifying the women at risk is a factor accounting for this lack of success and the introduction of a reliable biochemical marker would be of considerable value.

Relaxin is a polypeptide hormone that is produced in the corpus luteum and the placenta during pregnancy (Sherwood 1988). The main effects are well established in rats and guinea pigs in which it causes ripening of the uterine cervix, loosening of the pelvic girdle and maintenance of myometrial quiescence (Sherwood 1988). However, human relaxin has not been shown to inhibit pregnant human myometrial activity *in vitro* (Petersen *et al.* 1991), but local application of relaxin may induce cervical ripening (Evans *et al.* 1983; MacLennan *et al.* 1986). Results from in vitro studies suggest that relaxin may be associated with weakening of the fetal membranes (Koya *et al.* 1983).

The hypothesis of the present study was that high levels of serum relaxin might be associated with preterm delivery because of a ripening effect on the uterine cervix or a weakening of the fetal membranes. Thus, we investigated, whether a high serum level of immunoreactive human relaxin in the 30th week of pregnancy would identity women with an increased risk of spontaneous preterm delivery.

Subjects and methods

Women described in this case control study were identified from a cohort of women who were participating in a study of the relation between pregnancy outcome and the intake of certain dietary elements. The women in the cohort were recruited between 15 April 1988 and 15 January 1989 when visiting one of two antenatal clinics in Aarhus, associated with the University Clinic of Obstetrics and Gynecology, University of Aarhus. Those living in Aarhus town and in certain designated areas around the town, who were not likely to be moving from the area before labour and who were in the 30th week gestation, were eligible for the study. Prior to the visit to the antenatal clinic the women were informed in a letter about the

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investigation and were asked to participate. Of the 1203 women eligible, 991 (82%) accepted and they formed the study population.

The rate of preterm delivery in the study population was 3·3% and the rate of spontaneous preterm delivery, defined as spontaneous onset of labour, was 2·4%. A large number of well-educated women and a high socio-economic status in the study population may partly explain the low frequency of preterm delivery.

Serum samples were collected in the 30th week of gestation and stored at −50°C in plain polyethylene tubes for later analysis.

Data concerning previous pregnancies as well as the course of the current pregnancy, delivery and neonatal period became available later both for the participating women and for those who were eligible, but not participating in the study. All data were stored in a computer. The study was approved by the ethics committee of the County of Aarhus.

This particular investigation comprised all women ($n = 23$) who experienced a spontaneous preterm labour. None of these women had pre-eclampsia or small for gestational age babies. Since the blood samples were originally collected for another purpose, the remaining volume was insufficient in four samples and one sample was inexplicably lost, thus only 18 women with spontaneous preterm labour could be included in this study.

Due to limited capacity of the assay the number of women in the control group was fixed at 46. A random selection of these women was obtained by a computer. When the sample was missing or the volume was too small for analysis the next number was chosen instead. None of the women included in the present study had ovulation induced.

Serum samples were thawed and relaxin concentrations were determined in duplicate by a Human Relaxin Serum ELISA Kit (Genentech, Inc.). The method has been described in detail previously (Lucas *et al.* 1989) and will only be summarized briefly. Microtitre plates were coated for 24 h at 4°C with 100 µl purified rabbit antibody (0·48 mg/ml) raised against a synthetic human relaxin analogue (hRLX-2). After washing the plates with phosphate-buffered saline (PBS) containing 0·05% Tween-20 (wash buffer) the excess binding sites were blocked by 200 µl wash buffer containing 0·5% bovine serum albumin (BSA) for 1 h followed by repeated washing. After the addition of non-immune goat IgG (20 mg/ml) to all the serum samples as well as to the standards (20–1250 pg/ml), 100 µl of each were pipetted into each well, and the plates were incubated for 24 h at 4°C. After washing, the wells were then incubated with 100 µl of horse radish peroxidase- (HPR) conjugated antibody to synthetic human relaxin (diluted 1:3000 in wash buffer containing 0·5% BSA) for 4 h followed by repeated washing. A 100 µl volume of an orthophenylene diamine substrate (0·2 mg/ml) was added to each well and incubated for 20 min at room temperature. The reaction was stopped with 100 µl of 2·25 M H_2SO_4 and the absorbance was read at 492 nm. Data were computerized and sample concentrations were interpolated from the standard curve.

The intra-assay coefficient of variation was 17·3% when two samples were tested six times each in the same assay. The inter-assay coefficient of variation was 23·6% when 46 samples were tested twice in two different assays. All samples in the present study were tested in one assay.

Definitions

Preterm labour. Delivery <37 weeks gestation, gestational age was assessed from the duration of amenorrhoea complemented by early ultrasound when appropriate.

Pre-eclampsia. Blood pressure ≥140/95 mmHg developed after 20 weeks and proteinuria ≥0·3 g/l.

Small for gestational age. Birthweight <10% centile. The expected weight for gestational age was calculated as $\alpha + \beta$ (GA–280). Where GA is the gestational age in days at birth, α is the expected weight at term and β is the weight gain per day. For males $\alpha = 3437$ g and for females $\alpha = 3322$ g; for males $\beta = 28{\cdot}72$ g and for females $\beta = 27{\cdot}27$ g (Secher *et al.* 1986).

Statistics

The t test for unpaired observations was used for the comparison of group means of serum relaxin. The association between serum relaxin and gestational age was estimated by a linear regression by the method of weighted least squares. For the comparison of group proportions the χ^2 test was used. A significance level of 5% was chosen.

Results

There were no significant differences between the study population and the women who did not want to take part in the study in the following characteristics (the mean, SD values are shown for the study population): age (29, SD 4 years); gestational age at delivery (282, SD 12 days); birthweight (3491, SD 540 g); or the frequency of pre-eclampsia (1·3%), spontaneous preterm labour (2·4%) and small for gestational age babies (6·4%).

From Table 1 it can be seen that the distribution of age and parity did not differ significantly between cases and controls. Thus, the mean relaxin concentration in cases and controls were not adjusted for parity. The immunoreactive serum relaxin in the 30th week of pregnancy was significantly higher in the cases than in the controls (mean 455, SD 169 pg/ml (75, SD 7 mmol/l) *vs* 327, SD 139 pg/ml (54, SD 4 mmol/l); $P = 0{\cdot}003$) (Fig. 1) When primiparous women were considered separately, this difference was even more pronounced (Table 1).

Figure 2 shows the relation between serum relaxin concentrations in the 30th week and length of gestation at delivery in the 18 cases, the higher concentrations were associated with the shorter lengths of gestation ($r = -0{\cdot}53$, $P = 0{\cdot}02$). The seven women with preterm prelabour rupture of membranes had higher mean relaxin concentrations in the 30th week of pregnancy than the other 11 women (509 pg/ml *vs* 420 pg/ml) although the difference was not statistically significant ($P = 0{\cdot}08$).

There was no correlation between serum relaxin and length of gestation at delivery in the control group.

Discussion

The present study shows relaxin concentrations in normal

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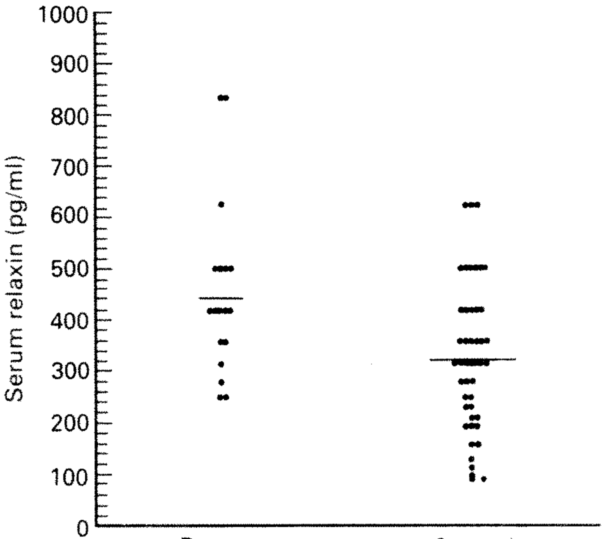

Fig. 1. Concentration of serum immunoreactive human relaxin (pg/ml) in the 30th week of pregnancy in 18 women with spontaneous preterm delivery (<37 weeks) compared with 46 delivered at term. The mean values (SD) were 454 (169) and 327 (139), respectively (P = 0·003, t-test for unpaired observations). The mean serum relaxin concentration in each group is indicated by a horizontal line.

pregnant women in the 30th week of pregnancy that are similar to those obtained by a homologous RIA (Bell *et al.* 1987). However, women having a preterm delivery had increased mean concentrations of serum immunoreactive human relaxin at this gestational age (Fig. 1) i.e., several weeks before the actual delivery.

It has been suggested previously that low peripheral concentrations of immunoreactive relaxin, as determined by a heterologous RIA based on porcine relaxin, were associated with preterm labour (MacLennan *et al.* 1986). Serial blood samples taken during the last weeks of pregnancy showed declining, very low relaxin concentrations in one woman who subsequently had a preterm labour and it was proposed that low relaxin levels caused a decreased suppression on the myometrial activity (MacLennan *et al.* 1986). Another study, however, showed increased values of immunoreactive human relaxin concentration in the 30th week of pregnancy in two of the three women delivered preterm when compared with corresponding values obtained in women delivered at term (Bell *et al.* 1988). Furthermore, women who became pregnant after stimulation with clomiphene citrate, human menopausal gonadotrophin and human chorionic gonadotrophin and subsequent in vitro fertilization have both very high immunoreactive serum relaxin concentrations and a very high frequency of preterm labour (Bell *et al.* 1989).

Table 1. Distribution of age and parity, gestational age, birthweight and serum relaxing concentrations among cases and controls

	Preterm (n = 18)	Controls (n = 446)	Significance (P)
Age (years)	26 (4)	28 (4)	0·09*
Parity			
Primiparous	13 (72%)	31 (67%)	0·7†
Multiparous	5 (28%)	15 (33%)	
Gestational age at delivery (days)	247 (10)	285 (9)	
Birthweight (g)	2519 (370)	3538 (638)	<0·0001*
Serum relaxin (pg/ml)			
All	455 (169)	328 (139)	0·003*
Primiparous	500 (203)	342 (98)	0·002*
Multiparous	335 (148)	298 (178)	0·6*

Results are mean (SD) and n (%) values as appropriate.
*t-test; †χ^2-test.

Confounder control was not performed in the present study because of the small number of cases. However, the two groups did not differ significantly in age or parity and did not include women with previous preterm labour, previous conization or clinical signs of infection. Vaginal bleeding during pregnancy occurred in two of the women with preterm delivery and they had serum relaxin concentrations of 417 pg/ml and 278 pg/ml. Decreased collagen synthesis and increased collagen breakdown in the cervix and fetal membranes may be important if relaxin causes preterm labour (Koya *et al.* 1983; Unemori & Amento 1990). Relaxin concentrations in women with preterm prelabour rupture of the membranes (PPROM) were higher than those obtained in women with spontaneous preterm delivery without PPROM and this may be due to a relaxin induced weakening of the fetal membranes (Koya *et al.* 1983).

The present study does not permit any firm conclusions on the value of serum relaxin as a biochemical marker for preterm labour. However, the results indicate, that increased relaxin concentrations might be associated with preterm labour. The results of the present preliminary study need to be confirmed and large scale serial studies are necessary to investigate whether relaxin concentrations are permanently elevated during pregnancy or rise shortly before the preterm labour.

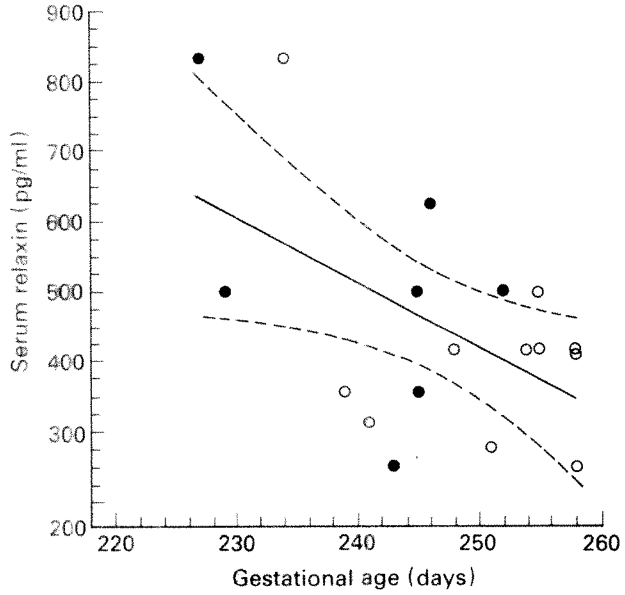

Fig. 2. Relation between serum immunoreactive human relaxin (pg/ml) in the 30th week of pregnancy and the length of gestation at delivery in 18 women with spontaneous preterm delivery (<37 weeks). The filled symbols represent women with preterm prelabour rupture of the membranes. The solid line represents the regression line and the dotted lines the 95% confidence interval of the regression line. r = −0·53, P = 0·02.

Acknowledgment

We thank Genentech Inc. for kindly providing the human relaxin ELISA kit.

This study was supported by grants from the Danish Medical Research Council, Sundhedsfonden, Helsefonden and Aarhus University Research Foundations. Dr K. Skajaa is a recipient of a fellowship from Novo Nordisk Foundation, Copenhagen, Professor Niels Jørgen Secher is thanked for valuable support.

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Received 18 April 1991
Accepted 29 October 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 296–301

FETAL AND NEONATAL MEDICINE

The effect of intrauterine growth retardation on the development of renal nephrons

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ABSTRACT

Objective To investigate the effect of Type II (asymmetrical) intrauterine growth retardation (IUGR) on renal development.

Design A prospective descriptive study.

Setting Department of Fetal and Infant Pathology, Liverpool Children's Hospital.

Subjects Six (severely) affected IUGR stillbirths of known gestational age with a control group of stillbirths with birthweight > 10th centile, and eight liveborn IUGR infants who died within a year of birth with a control group of appropriately grown infants who died within a year of birth (postnatal groups).

Techniques The kidneys from all the groups studied were analysed using unbiased, reproducible and objective design-based stereological techniques.

Main outcome measures Total renal nephron (glomerular) numbers and average volumes of total nephron and cortical and medullary nephron segments.

Results Nephron number estimates lay below the control group's 5% prediction limit in five out of the six growth-retarded stillbirths, and were significantly ($P<0{\cdot}005$, IUGR at 65% of the control mean) reduced in the postnatal group. Estimates of nephron (segment) volume did not differ between control and IUGR groups.

Conclusions Type II intrauterine growth retardation may exert a profound effect on renal development. The reduced nephron number at birth, together with the lack of any early postnatal compensation in either nephron number or nephron size, emphasizes the need for vigorous antenatal surveillance for IUGR and consideration of elective preterm delivery of affected fetuses. A systematic review of other organs, which develop in a similarly rapid fashion during the late intrauterine period, is indicated by this work. With one exception, all birthweights in the growth-retarded groups were below the third centile, thus the precise quantitative relation between progressive IUGR and renal function requires further assessment.

Intrauterine growth retardation (IUGR), defined as a birthweight below the 10th centile for gestational age (Battaglia & Lubchenco 1967), is associated with a perinatal mortality of up to 12 times (Usher & McLean 1974) greater than that observed when a birthweight is appropriate for gestational age. Perinatal morbidity is similarly increased by a factor of three (Lin 1985). Approximately 7% of stillbirths (Magani *et al.* 1990) and from 2 to 8% of livebirths (Hobbins & Berkowitz 1977) are affected, and 80% of all cases are classified as Type II IUGR (Kurjak *et al.* 1978).

The infant with Type II (asymmetrical) IUGR is characterized by a disproportionately large head, small abdominal viscera and a lack of subcutaneous fat (Usher & McLean 1974). As this form of growth retardation is unusual before the third trimester (Campbell 1976), when fetal growth has shifted from a phase of cellular hyperplasia and organogenesis to one of predominantly cellular hypertrophy (Winick & Noble 1965), individual organ deficits are thought to represent a reduction in cell size rather than in cell number (Usher & McLean 1974).

However, 'organogenesis' of the kidney, in the context of the development of functional units i.e., nephrons, continues into the third trimester with the induction of approximately 60% of the normal complement of nephrons occurring during this period (Hinchliffe *et al.* 1991a). One may hypothesize, therefore, not only qualitative but perhaps also quantitative nephron defects in the kidney in Type II IUGR. Furthermore, as induction of nephrons ceases under normal circumstances by about 36 weeks gestation (Hinchliffe *et al.* 1991a; Osathanondh & Potter 1963), the postnatal compensatory growth phase, commonly seen in infants with this form of growth retardation and presumably reflecting (delayed) cellular hypertrophy, may produce only a limited improvement in renal function, based on increased cellular or nephron size rather than

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increased nephron number. Although no prolonged presence of nephrogenic tissue has been seen in IUGR, suggesting arrest rather than delay of glomerular development, some aspects of retained immaturity, such as 'immature' or 'fetal-appearing' glomeruli, have been reported (Wigglesworth 1984) in infants with established disturbed antenatal development. Thus the precise manner in which IUGR may affect renal development requires further clarification.

Recent advances in design-based stereology have permitted, for the first time, the unbiased estimation of total renal nephron number (Sterio 1984; Gundersen 1986; Howard 1990). As we have demonstrated (Hinchliffe *et al.* 1991a) one may also obtain an indication of the average volume of the developing cortical and medullary nephron segments and hence attempt to quantify the development and maturation of the nephron. To analyse the effects of Type II growth retardation on the development of the kidney, in view of a possible contribution of renal insufficiency to IUGR-associated mortality and morbidity, we applied these novel stereological techniques to a group of stillbirths and liveborn infants who demonstrated features of asymmetric IUGR.

Subjects and methods

The following case groups were collected consecutively.

Prenatal period

Type II IUGR. This group included six non-macerated stillbirths, of accurately determined gestational age, with birthweights below the 10th centile and displaying features of Type II IUGR.

Controls. The control group included non-macerated, third trimester stillbirths of accurately determined gestational age, with birthweights above the 10th centile and without congenital malformations. This group was expanded anteriorly with similarly selected second trimester miscarriages ($n = 11$), again with certain gestational age.

Postnatal period

Type II IUGR. This group included eight infants who died in the postnatal period (within one year of birth) and whose birthweights had been below the 10th centile for the accurately determined gestational age. All the infants had features of Type II IUGR at birth and at post-mortem examination.

Controls. The control group comprised seven infants who died in the postnatal period and whose birthweight had been above the 10th centile for the accurately determined gestational age, none of them had any congenital malformations.

The disector method for the unbiased estimation of total renal nephron (glomerular) number

The disector method (Sterio 1984) uses two parallel histological sections (a 'disector pair'), separated by a distance less than the minimum glomerular diameter, as a three-dimensional probe for the estimation of zero-dimensional cardinality. By counting those glomerular profiles seen in the first (reference) but not in the second (look-up) section, the number of glomeruli related to the sample volume between the two sections is established. Repeating this procedure over a systematically randomized series of disector pairs, throughout the kidney, provides the cortical glomerular numerical density, N_v(glom/cortex). The product of this and the total cortical volume, V(cortex), estimated by the classic point-counting principle of Cavalieri (Sterio 1984; Gundersen & Jensen 1987), is the total renal glomerular number:

$$N(\text{glom}) = N_v(\text{glom/cortex}) \times V(\text{cortex})$$

Using the same stereological methods, the quotients V(total)/N(glom), V(cortex)/N(glom) and V(medulla)/N(glom), where V(total) and V(medulla) are the total renal and medullary volumes respectively, can be derived. These estimates of average total nephron-, cortical nephron segment- and medullary nephron segment volume (more precisely the average 'domains' associated with the nephron and its cortical and medullary segments), will be biased by the shrinkage accompanying histological processing. However, trend differences between groups of these variables may be usefully analysed (Hinchliffe *et al.* 1991a) as approximately the same degree of shrinkage will occur in all specimens, in view of the similar size/volume range and the identical fixation and processing methods.

Specimen selection and tissue processing

On the basis of the stereological results of the prenatal control group, in which both left and right kidneys were analysed and which are discussed elsewhere (Hinchliffe *et al.* 1991a), it was considered sufficient to study only one kidney, randomly selected (throwing a die: odd number selecting left kidney, even number selecting right kidney) in the postnatal control group. Similarly, and assuming a symmetrical effect of IUGR, only one kidney, randomly selected, was used in both pre-and postnatal IUGR groups.

Kidneys of the prenatal groups were fixed in 0·1 M sodium phosphate-buffered formaldehyde (pH 7·4, 4% formaldehyde) for a minimum of 48 h, before being embedded whole in paraffin, using routine procedures in a Histomat tissue processor.

Kidneys of the postnatal groups were fixed in 0·1 M sodium phosphate-buffered formaldehyde (pH 7·4, 4% formaldehyde) for a minimum of 48 h, before being sectioned into slices of equal thickness. Slices were embedded separately in paraffin using routine procedures in a Histomat tissue processor.

Section preparation

'Disector pairs' of 5μm, haematoxylin and eosin stained histological sections were prepared as described elsewhere (Hinchliffe *et al.* 1991a).

Estimation of the total number of glomeruli in the cortex

An unbiased estimate of the total number of glomeruli in the cortex of each kidney, N(glom), was calculated (Sterio 1984; Gundersen 1986):

$$N(\text{glom}) = N_v(\text{glom/cortex}) \times V(\text{cortex})$$

The coefficient of error of each glomerular number estimate was calculated according to Braendgaard *et al.* (1990) and found to be $<10\%$ for every estimate.

Nephron volume estimation

Estimation of the average volume of (i) the (whole) nephron including its glomerulus (ANV); (ii) the cortical segment of the nephron including its glomerulus, (ACNV) and (iii) the medullary segment of the nephron (AMNV) were calculated as follows:

$$\text{ANV} = \text{V(total)/N(glom)}$$
$$\text{ACNV} = \text{V(cortex)/N(glom)}$$
$$\text{AMNV} = \text{V(medulla)/N(glom)}$$

Statistical analysis

The difference between the mean values of the total glomerular number estimates in the postnatal control and IUGR groups was analysed using the two-tailed, two-sample *t*-test (Bland 1987).

The relations between N(glom) and gestational age for the control group, and between ANV, ACNV and AMNV and postnatal age for control and IUGR groups were analysed by multiple regression using least squares procedures. The techniques are described by Bland (1987) and were performed using the SAS statistical package (SAS Institute Inc. 1985).

Results

The birthweights of the five male and one female fetuses in the prenatal, IUGR group are shown in Fig. 1. Weights at birth and death of the male and female infants in the postnatal, IUGR group are shown in Fig. 2.

The renal weights in the prenatal, IUGR and control groups are given in Fig. 3. Renal weights in the postnatal control and IUGR groups are shown for males and females in Fig. 4a and b respectively.

The relations between the total glomerular number, N(glom), and age for both the prenatal and postnatal groups are shown in Fig. 5a and b respectively. In the postnatal group, the mean glomerular number in the IUGR infants is highly significantly ($P < 0{\cdot}01$) lower (65% of the control mean) than that of the control infants.

The relations between the average total nephron volume, ANV, and age for both the prenatal and postnatal groups are shown in Fig. 6a and b respectively. The regression line and 95% prediction limits for the control population are given. The probability of these results, if there is no difference in slope and intercept between postnatal control and IUGR groups, is: $P = 0{\cdot}85$ and 0·88 respectively. Similarly, for ACNV: $P = 0{\cdot}71$ and 0·68, for AMNV: $P = 0{\cdot}72$ and 0·63 (data not shown).

Discussion

The chief finding of the present study is a reduction of total glo-

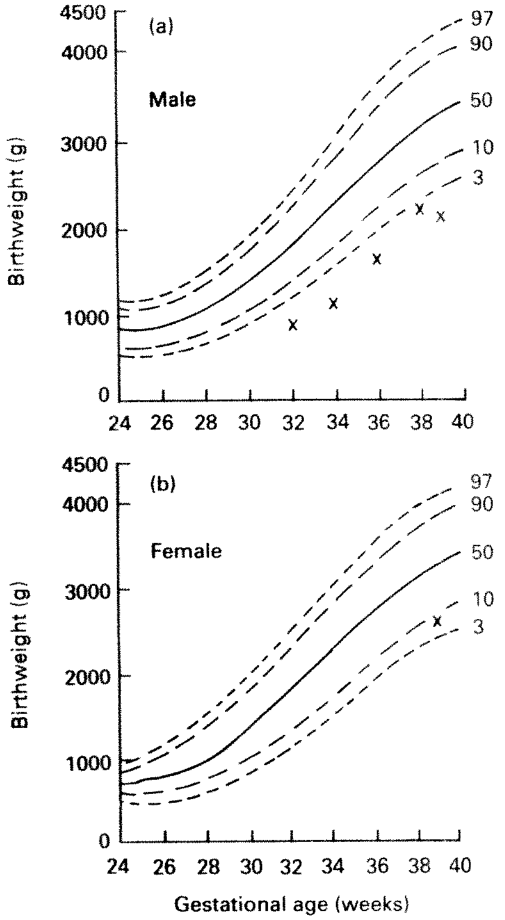

Fig. 1. Smoothed centiles (adapted from Yudkin *et al.* 1987) of birthweight and gestational age, showing the birthweights (crosses) of five male (a) and one female (b) in the prenatal IUGR group.

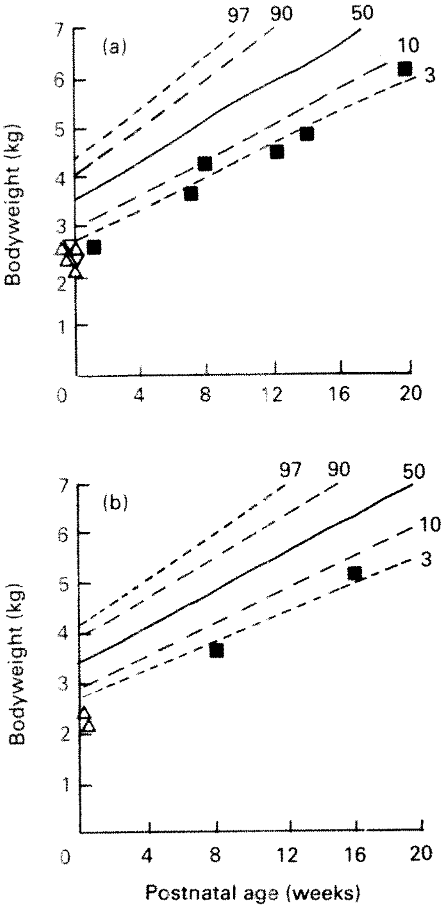

Fig. 2. Smoothed centiles (adapted from Tanner *et al.* 1987) of birthweight and postnatal growth, showing the weights at birth (△) and death (■) of six male (a) and two female (b) infants in the postnatal IUGR group.

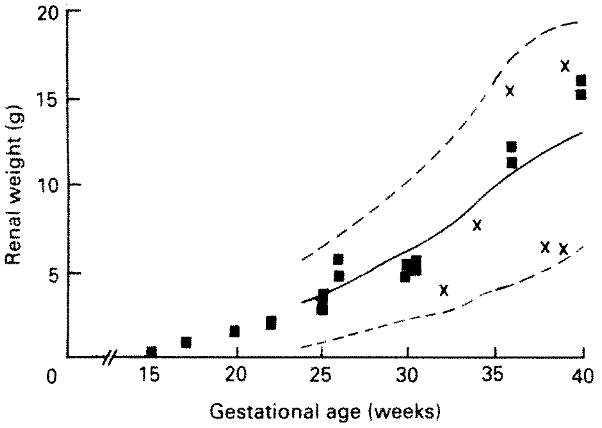

Fig. 3. Smoothed centiles (adapted from Gruenwald & Minh 1960) of renal weight and gestational age, showing the renal weights in the prenatal control (■) and IUGR (×) groups.

merular, i.e., nephron, number in five of six stillbirths with Type II IUGR (Fig. 5a). This may contribute to the increased perinatal morbidity and mortality seen in liveborn infants with IUGR, as a limitation of renal functional reserve may compromise the homeostasis of the individual. Indeed, a reduced glomerular filtration capacity, in addition to helping explain the intrauterine renal failure reported (Steele *et al.* 1988) in fetuses with severe Type II IUGR, may facilitate understanding of cases where the degree of postnatal renal failure was not fully explained by the severity of perinatal asphyxia. The situation is in some aspects comparable to that of unilateral renal agenesis in which the limitation of renal capacity does not, under normal physiological circumstances, result in increased plasma concentrations of urea or creatinine. However, during periods of acute, severe homeostatic stress, such as encountered in perinatal intensive care situations, a limited functional reserve may be expected to be of clinical relevance. Similarly, combined viral and bacterial infection with septicaemia and shock may manifest a reduced homeostatic capacity, especially during the first few months of life when compensatory nephron changes have as yet not occurred (Fig. 6b).

The magnitude of the difference in total nephron number between control and IUGR groups highlights the sensitivity of the developing kidney to impaired nutritional supply during the period of nephron induction, if one accepts deficient nutrition of the renal blastema as a final common pathway for under-development. In this regard, one may hypothesize that the growth-retarded fetus with a normal complement of nephrons (Fig. 5a, gestational age 36 weeks) had been subject to

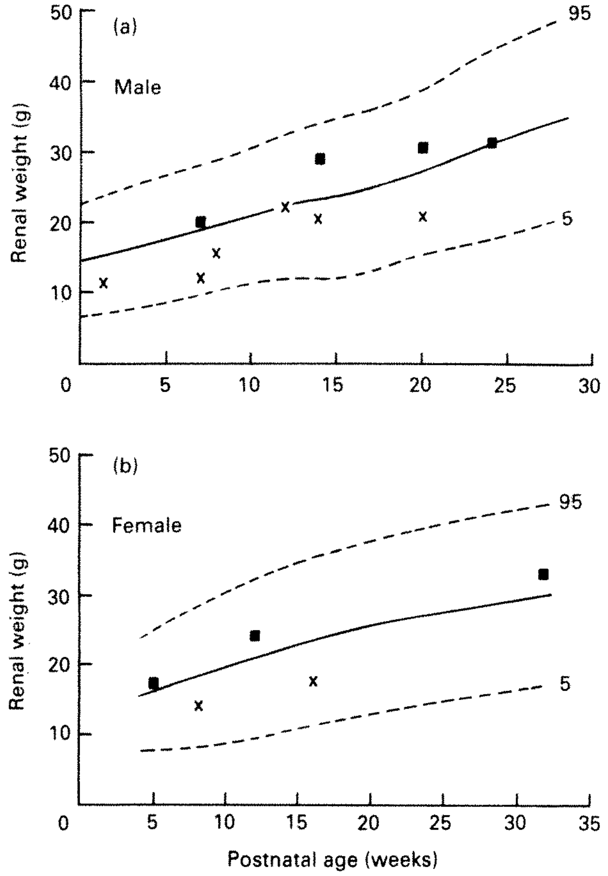

Fig. 4. Smoothed centiles (adapted from Schulz *et al.* 1962) of renal weight and postnatal age showing the renal weights of the male (a) and female (b) infants in the postnatal control (■) and IUGR (×) groups.

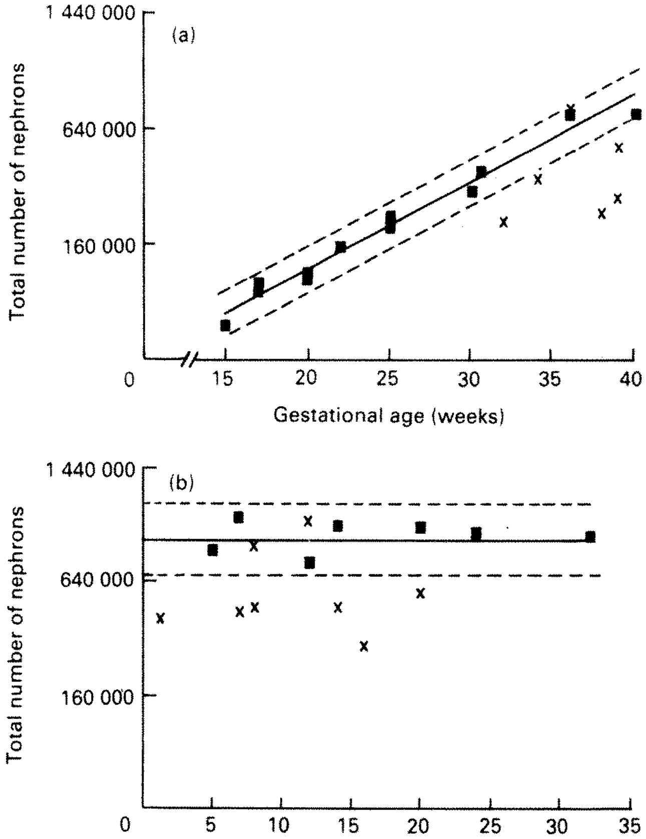

Fig. 5. (a) Relation between the total glomerular i.e., nephron number, N(glom) (y-axis, square root plot), and gestational age (x-axis) for the prenatal control and IUGR groups. The regression line and 95% prediction intervals for the control group are plotted. (b) Relation between the total glomerular i.e., nephron number, N(glom) (y-axis, square root plot), and postnatal age (x-axis) for the postnatal control and IUGR groups. The mean (2SD) for the control group is shown. The difference in number between control and IUGR groups was highly significant: $P<0{\cdot}005$ (two-tailed, two-sample *t*-test). (■) = control; (×) = IUGR.

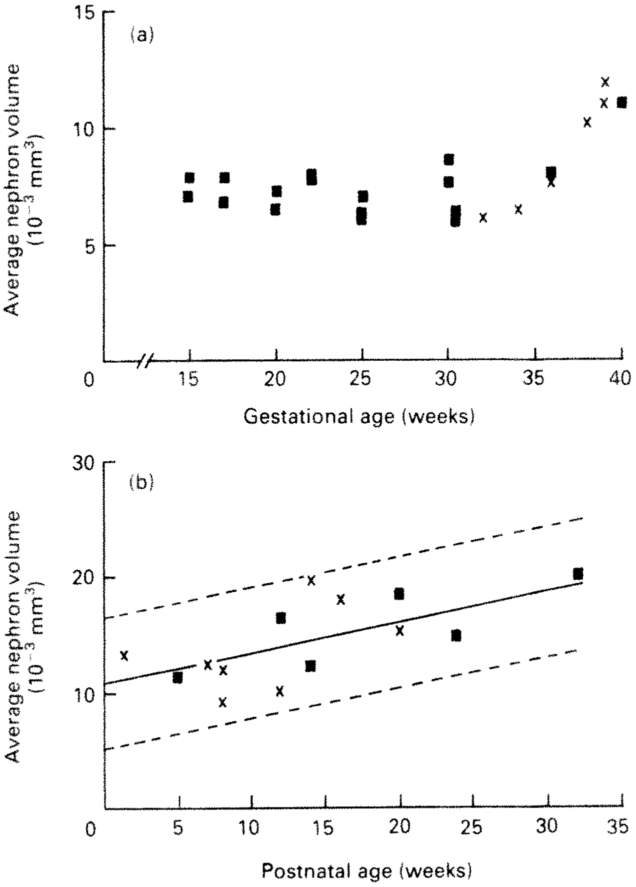

Fig. 6. (a) Relation between the average total nephron volume (y-axis), ANV, and gestational age (x-axis) for the prenatal control and IUGR groups. (b) Relation between ANV (y-axis) and postnatal age (x-axis) for the postnatal control and IUGR groups. Probability of these results if there is no difference in slope and intercept between postnatal control and IUGR groups is $P = 0{\cdot}85$ and $0{\cdot}88$ respectively (multiple regression). The regression line and 95% prediction intervals for the control population are plotted. (■) = control; (×) = IUGR.

acute, severe but late-onset IUGR; a process which could result in a similar (reduced) birthweight to that associated with a more insidious insult occurring before the loss of the nephrogenic zone and reflected, therefore, in a low number of nephrons.

The absence, postnatally, of a significant compensatory nephron number increase in Type II IUGR (Fig. 5b) causes concern as it contradicts the general opinion that, when peri- and postnatal complications can be avoided, IUGR is not associated with permanent damage.

We feel that these findings emphasize the clinical importance of early prenatal diagnosis in this condition, and provide additional support for the view of other investigators (Chiswick 1985; Neligan *et al.* 1976; Vohr *et al.* 1979) that prenatal therapy or elective preterm delivery of affected fetuses should be considered, to facilitate a resumption of renal development by improving the general fetal condition before the loss of the nephrogenic zone. The apparent lack of any compensatory intrauterine hypertrophy in the individual nephron segments (Fig. 6a) should be interpreted similarly.

As the average volumes of the individual nephron components do not differ significantly between control and IUGR kidneys over the period studied (Fig. 6), the spatial distribution of glomerular profiles seen in histological sections would be similar. This may explain the conclusions reported by Wigglesworth (1984), based in part on glomerular profile patterns, that IUGR seems not to affect renal development. Furthermore, as the last 400 000 nephrons develop with the emergence of the two most sub-capsular generations of glomeruli, a considerable reduction in nephron number may go unnoticed using the technique of glomerular generation counting, since both intra-and inter-observer reproducibility of the method during this period of renal development are limited (Hinchliffe *et al.* 1991b). It is of interest that the kidneys in growth-retarded individuals were of 'low normal' weight defined against current tables for normal values; illustrating, as discussed by Hinchliffe *et al.* (1991a), the limited potential of renal weight as an index for the detection of abnormal development, whilst emphasizing the potential of modern stereology for elucidating quantitative aspects of both normal and abnormal development.

In summary we conclude that, at least when of a severe nature, Type II IUGR may exert a profoundly deleterious effect on the development of the kidney. The lack of any significant compensatory increase in either nephron number or nephron size, during the early phases of postnatal life, highlights the need for vigorous antenatal surveillance for IUGR. One may predict renal development in affected fetuses to benefit from elective preterm delivery. A systematic review of other organs such as the lung and central nervous system, which develop in a similarly rapid fashion during the late intrauterine period, is indicated by this work. The abnormalities demonstrated were found, with one exception, in severe Type II IUGR (birthweight < 3rd centile), and the precise quantitative relation between a progressive reduction in nephron number and its encroachment on renal reserve capacity similarly requires further elucidation in clinical studies. Early results on comparing quantitative measures of renal growth by ultrasound with measures of renal function (Deutinger *et al.* 1987) indicate the feasibility of *in utero* assessment of functional limitations of the renal system, which, even when not essential to intrauterine life, may then be used to modulate therapy in the newborn period.

Acknowledgment

The authors wish to acknowledge the expert statistical assistance of Dr J. L. Hutton and the histological expertise of Ms Fiona McGill and Miss Elizabeth Hughes.

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Received 11 July 1991
Accepted 6 November 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 302–306

FETAL AND NEONATAL MEDICINE

A randomized controlled trial to compare three types of fetal scalp electrode

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ABSTRACT

Objectives To compare three scalp electrodes in respect of need for reapplication, trace quality and scalp trauma.

Design Randomized controlled trial.

Setting Maternity Unit, Royal Berkshire Hospital, Reading.

Participants 780 women in labour at term, with cephalic fetal presentation, deemed to require electronic fetal heart rate monitoring using a scalp electrode.

Interventions Three types of fetal scalp electrode: Rocket-Rolon (double-helix spiral); Hewlett-Packard (double-helix spiral); and Surgicraft-Copeland (clip).

Main outcome measures Need for more than one electrode; reason for replacement; trace quality; scalp trauma; direct financial costs.

Results Reapplication was significantly least likely in the Surgicraft-Copeland group (odds ratio *vs* Hewlett-Packard = 0·61, 95% CI 0·41–0·90; odds ratio *vs* Rocket-Rolon = 0·43, 95% CI = 0·29–0·62). This reflected a much lower rate of replacement because of detachment. The Hewlett-Packard was, however, least likely to be replaced because of poor trace quality. Interpretable traces were equally common, but trace quality tended to be superior in the Hewlett-Packard group. There was no serious scalp trauma. Difficulty removing the electrode was least often reported in the Hewlett-Packard group, and a mark on the scalp persisted least often in the Rocket-Rolon group.

Conclusions The Surgicraft-Copeland performed the best overall, and particularly in respect of attachment to the scalp. It appears to be the electrode of choice of the three tested.

Fetal monitoring with a scalp electrode is commonly used during labour to provide a continuous recording of the heart rate. There are several different types of electrode, but no consensus about which performs best. The principal differences between the electrodes are in the mechanism by which they are attached to the fetal scalp. Spiral electrodes which may be a single helix (for example, the Corometrics electrode), or double helix (for example, the Rolon electrode manufactured by Rocket, and the Hewlett-Packard electrode), are applied with an applicator and attached by a screwing action. The Surgicraft-Copeland electrode has a skin clip on a small disc (Ghosh & Tipton 1976). The clip is spring-loaded in a closed position but once the disc is apposed to the fetal scalp the clip can be opened by twisting the body of the electrode and then released to secure attachment.

The study reported here was prompted by an observation made by midwives at the Royal Berkshire Maternity Unit that the Rocket-Rolon fetal scalp electrode then in routine use frequently needed replacing several times during the course of a single labour. Informal introduction of alternative electrodes suggested that these might perform better. To test whether this was true, a large randomized controlled trial was mounted to compare the three electrodes (Rocket-Rolon, Hewlett–Packard and Surgicraft-Copeland) that are most commonly used within the UK.

Subjects and methods

The trial was conducted at the Maternity Unit of the Royal Berkshire Hospital during a 7-month period in 1988. The study design was approved by the research and ethics committee for the West Berkshire Health District.

The principal aims of the study were to assess which of the three electrodes (i) required least frequent reapplication throughout the progress of a woman's labour; (ii) best maintained a good quality trace of the fetal heart rate pattern; and (iii) caused the least trauma to the baby's scalp.

Steps were taken to minimize the possibility that previous experience with one particular electrode might influence the outcome of the study. First, the midwives were instructed in the correct method of application of each type of electrode; and second, during a 3-month training period before the trial, each device was used systematically for one month according to the manufacturer's instructions.

All women, booked to be delivered in the hospital, were given a letter in the last trimester of pregnancy seeking their

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collaboration in the study. It mentioned that the standard policy of monitoring for low-risk labours was intermittent auscultation and emphasized that an electrode would only be applied if there were a medical indication for electronic fetal monitoring, for example, if labour was artificially induced or epidural analgesia was in progress. The women were also assured that none of the electrodes was known to be less reliable than the others and that a decision not to participate would not jeopardize their care in any way.

Recruitment took place on the labour ward. Women were eligible for entry to the trial if (i) the fetus was a singleton and presenting cephalically, (ii) the gestation was more than 37 completed weeks, and (iii) a decision had been made to apply a scalp electrode. At the time of the study, the routine policy in the hospital was to apply a scalp electrode once a decision had been taken to monitor labour electronically; an external transducer was only used if it was not possible to monitor labour satisfactorily with a scalp electrode. The monitors used were Hewlett-Packard 80/30As and 80/40As. Of the 3316 women who were delivered during the study period, 802 fulfilled these entry criteria and 780 (97%) of them were subsequently recruited to the study. The commonest reasons for non-recruitment were that the midwife forgot the trial, and that labour advanced too rapidly. Entry to the trial, which was signalled by opening the next in a series of consecutively-numbered sealed opaque envelopes, occurred at the time a decision was made to apply a fetal scalp electrode.

Once the envelope seal was broken, the woman had irrevocably entered the trial. To minimize selection bias a woman remained in the study group allocated for the purpose of analysis, regardless of subsequent management. If a woman was recruited into the study but the envelope remained unopened, the midwife was asked to note the reason why.

Each envelope contained a random allocation to one of the following electrodes throughout the course of a labour: Rocket-Rolon, Hewlett-Packard or Surgicraft-Copeland. Random allocation was computer-generated in balanced blocks that randomly varied in size between 3 and 15.

Data describing the women at trial entry and the subsequent performance of the scalp electrodes were recorded during labour. The midwives were asked to record the date, time and reason for the initial, and each subsequent, electrode application. They also noted the position and dilatation of the cervix, and whether or not an application was accomplished at the first attempt. The experience of operators was assessed by their status and by the number of times they had previously applied a particular electrode. The total number of vaginal examinations throughout labour, and whether or not a fetal blood sample had been obtained, were also recorded, as these procedures may affect the performance of an electrode or may themselves be affected by the performance of an electrode. Following delivery, the midwives noted any problems with removal of the device, and the degree of any trauma to the baby's scalp.

Scalp trauma was reassessed by community midwives (who were unaware of the group allocation) on the 10th day postpartum, when the mothers were asked to record their experiences and opinions in relation to the use of the electrodes.

At the end of the study the quality of each cardiotocographic recording was assessed by an obstetrician (G.H.) who was 'blind' to the trial allocation. The recording for each stage of labour was graded for quality and total duration of trace. Each trace was divided into sections of 'good' quality, 'adequate' quality, 'poor' quality and 'external' (recorded via an abdominal transducer) recording. A good quality trace had minimal signal loss or artefactual recording, and could be interpreted easily. An adequate quality trace had some signal loss or artefact but could still be interpreted. A poor quality trace had so much signal loss or artefact that it could not be interpreted. The length of time in the trial with 'no tracing' was calculated by subtraction. The type and age of the monitor was also noted.

A sample size of 750 women was pre-specified. This was based on an expected reapplication rate for the Rocket-Rolon electrode of 50%. A trial of this size would have an 80% (β error 0·20) likelihood of identifying a reduction to 37·5% associated with one or other alternative electrode (α = 0·05).

Results

Table 1 describes the 780 women recruited to the trial and demonstrates the comparability of the three groups generated by randomization. Overall, the main reasons for the initial scalp electrode attachment were a fetal heart rate abnormality suspected from external auscultation (43%), meconium-stain-

Table 1. Description of groups at trial entry

	Rocket-Rolon (*n* = 260)	Hewlett-Packard (*n* = 261)	Surgicraft-Copeland (*n* = 259)
Maternal age (years) mean [SD]	26·3 [5·2]	27·0 [5·2]	26·3 [5·2]
Primiparous *n* (%)	174 (67)	180 (69)	178 (69)
Gestational age (weeks) mean [SD]	39·5 [1·7]	39·5 [1·9]	39·6 [1·5]
Birthweight (g) mean [SD]	3327 [532]	3349 [522]	3339 [522]
Length of labour before trial entry (min) median	184·5	178·0	199·0
(interquartile range)	(36·0–383·0)	(11·0–409·0)	(28·0–369·0)
Effective epidural *n* (%)	92 (35)	94 (36)	103 (40)
Reason for scalp electrode attachment *n* (%)			
Auscultated FHR abnormality	109 (42)	109 (42)	120 (47)
Meconium	77 (30)	90 (34)	74 (29)
Intravenous oxytocin	61 (23)	46 (18)	50 (19)
Suspected IUGR	12 (5)	16 (6)	14 (5)
Other	1 (0)	0 (0)	1 (0)

FHR = fetal heart rate; IUGR = intrauterine growth retardation.

Table 2. Details of first application

	Rocket-Rolon (*n* = 260) *n* (%)	Hewlett-Packard (*n* = 261) *n* (%)	Surgicraft-Copeland (*n* = 259) *n* (%)
Electrode actually used			
Rocket-Rolon	250 (96)	2 (1)	1 (0)
Hewlett-Packard	3 (1)	257 (98)	7 (3)
Surgicraft-Copeland	4 (2)	2 (1)	251 (97)
Not known	3 (1)	0 (0)	0 (0)
Operator			
Midwifery sister	90 (35)	88 (34)	99 (38)
Staff midwife	104 (40)	96 (37)	92 (36)
Doctor	64 (25)	68 (26)	61 (24)
Other	2 (1)	9 (3)	7 (3)
Operator experience (>20 applications)	150 (58)	135 (52)	139 (54)
Cervix posterior	86 (33)	88 (34)	89 (34)
Cervical dilatation <3 cm	43 (17)	40 (15)	42 (16)
Head above ischial spines	201 (77)	192 (74)	196 (76)
More than one attempt	41 (16)	43 (16)	42 (16)
Application			
Difficult	32 (12)	28 (11)	22 (8)
Impossible	15 (5)	11 (4)	7 (3)

ing of the amniotic fluid (32%), and intravenous oxytocin for induction or augmentation of labour (21%). Fourteen electronic fetal heart rate monitors were employed during the study and these were used equally frequently in the three trial groups.

Similar numbers of women in the three groups received the allocated electrode at the first application (Table 2). The type and previous experience of the operator, and the degree of difficulty of application, as judged by the position and dilatation of the cervix and by the station of the head, were also similar (Table 2). More than one attempt was needed for application for 16% of women but this did not differ between the groups. Application of the Rocket-Rolon electrode, however, was more often described as 'difficult' or proved impossible (Table 2) (odds ratio *vs* Surgicraft-Copeland = 1·75, 95% CI

Table 3. Description of the trial policies and performance of electrodes

	Rocket-Rolon (*n* = 260) *n* %	Hewlett-Packard (*n* = 261) *n* %	Surgicraft-Copeland (*n* = 259) *n* %
Types of electrode actually used			
Allocated electrode used throughout	232 (89)*	249 (95)*	247 (95)*
Allocated plus other electrode	18 (7)	9 (3)	5 (2)
Non-allocated electrode used throughout	10 (4)	3 (1)	7 (3)
No. of applications per labour			
1	161 (62)	183 (70)	206 (80)
2	70 (27)	62 (24)	41 (16)
3	23 (9)	16 (6)	10 (4)
4	5 (2)	0 (0)	2 (1)
5	1 (0)	0 (0)	0 (0)
Total applications	395	355	326
Reason for first replacement			
Poor or absent trace	26 (10)	12 (5)	24 (9)
Detachment	64 (25)	62 (24)	25 (10)
Other	9 (3)	4 (2)	4 (2)
Performance of electrode			
Not replaced			
Detached <5 min before birth, or after delivery	116 (45)†	130 (50)	142 (55)
Detached >5 min before delivery	40 (15)	46 (18)	52 (20)
Time of detachment not known	5 (2)	7 (3)	12 (5)
Replaced	99 (38)‡	78 (30)‡	53 (20)‡

*Rocket-Rolon *vs* Hewlett-Packard, χ^2 7·00, $P<0·01$. Rocket-Rolon *vs* Surgicraft-Copeland, χ^2 6·87, $P<0·01$.
†Rocket-Rolon *vs* Surgicraft-Copeland, χ^2 5·41, $P<0·05$.
‡Rocket-Rolon *vs* Hewlett-Packard, χ^2 3·90, $P<0·05$. Rocket-Rolon *vs* Surgicraft-Copeland, χ^2 19·44, $P<0·001$.
‡Hewlett-Packard *vs* Surgicraft-Copeland, χ^2 6·12, $P<0·02$.

Table 4. Labour, delivery and neonatal outcome

	Rocket-Rolon (n = 260) n (%)	Hewlett-Packard (n = 261) n (%)	Surgicraft-Copeland (n = 259) n (%)
Vaginal examinations—mean [SE]	3·84 [0·09]	3·79 [0·09]	3·68 [0·09]
Fetal blood sample taken	13 (5)	16 (6)	7 (3)
Mode of delivery			
Normal vaginal	163 (63)	173 (66)	185 (71)
Instrumental vaginal	69 (26)	65 (25)	50 (19)
Caesarean	28 (11)	25 (10)	24 (9)
Apgar score			
0–3	3 (1)	1 (0)	1 (0)
4–6	3 (1)	2 (1)	1 (0)
7–10	254 (98)	258 (99)	257 (99)
Electrode difficult to remove at delivery	12 (5)	3 (1)	10 (4)
Scalp trauma at delivery more than 'broken skin'	1 (0)	1 (0)	4 (2)
Scalp bleeding following delivery	16 (6)	13 (5)	17 (7)
Scalp trauma visible at 10 days postpartum	38/217 (18)*	59/224 (26)*	56/206 (27)*

*Rocket-Rolon *vs* Hewlett-Packard, χ^2 = 5·01, P = 0·025. Rocket-Rolon *vs* Surgicraft-Copeland, χ^2 = 5·72, P<0·025.

1·07–2·82; P<0·05); and women allocated to the Rocket-Rolon were significantly more likely to be monitored with one of the other electrodes at some time during labour.

Women in the Surgicraft-Copeland group were significantly least likely to need a reapplication (odds ratio *vs* Hewlett-Packard = 0·61, 95% CI 0·41–0·90; odds ratio *vs* Rocket-Rolon = 0·43, 95% CI = 0·29–0·62) (Table 3). The difference in reapplication rates persisted: a third application was necessary to 12 allocated to the Surgicraft-Copeland, to 16 allocated to the Hewlett-Packard, and to 29 women allocated the Rocket-Rolon electrode.

The Surgicraft-Copeland was much less likely to become detached (odds ratio *vs* Hewlett-Packard = 0·36, 95% CI 0·23–0·58; odds ratio *vs* Rocket-Rolon = 0·35, 95% CI = 0·22–0·55) whereas the Hewlett-Packard was least likely to be replaced because of poor or absent fetal heart rate trace (odds ratio *vs* Surgicraft-Copeland = 0·49, 95% CI 0·25–0·95; odds ratio *vs* Rocket-Rolon = 0·45, 95% CI 0·23–0·87). This pattern of reasons for reapplication also persisted.

The rate of success of the electrode in terms of persistent attachment to the fetal scalp up to at least 5 min before delivery was greatest in the Surgicraft-Copeland group (Table 3), and this was significantly higher than in the Rocket-Rolon group (odds ratio = 0·67, 95% CI 0·47–0·94).

The differences between the electrodes in the need for reapplication were reflected in the frequency of vaginal examination in the trial groups (Table 4); when compared with the Surgicraft-Copeland group, there were an extra 11 examinations for every 100 women monitored in the Hewlett-Packard group, and an extra 16 examinations per 100 women in the Rocket-Rolon group. The differences were not, however, statistically significant.

There were no clear differences between the groups in the use of fetal blood sampling, mode of delivery and low Apgar score, although fetal blood sampling, instrumental delivery and low Apgar score were least common in the Surgicraft-Copeland group (Table 4).

There was no serious scalp trauma. 'Difficult removal' was least often reported for the Hewlett-Packard electrode (odds ratio *vs* Surgicraft-Copeland = 0·33, 95% CI 0·11–0·99; odds ratio *vs* Rocket-Rolon = 0·29, 95% CI 0·10–0·81). Marks at the site of electrode insertion 10 days after delivery were significantly least commonly reported in the Rocket-Rolon group (Table 4) (odds ratio *vs* Surgicraft-Copeland = 0·57, 95% CI 0·36–0·90; odds ratio *vs* Hewlett-Packard = 0·60, 95% CI 0·38–0·93).

The type of fetal heart rate monitoring and the quality of the traces recorded using scalp electrodes, are summarized in Table 5. There was no difference between the electrodes in the length of interpretable trace ('good' and 'adequate' combined). However, interpretable traces were more often of 'good' quality in the Hewlett-Packard group. Similarly, there was no difference between the electrodes in the length of uninterpretable trace ('poor' quality or no trace), but an external

Table 5. Type and quality of fetal heart rate tracing

	Length of trace (min)		
	Rocket-Rolon	Hewlett-Packard	Surgicraft-Copeland
Good or adequate quality tracing from scalp electrode	163 [80, 261]	164 [78, 291]	157 [89, 280]
Poor quality tracing or no trace	23 [1, 44]	19 [8, 39]	22 [10, 43]
Via external transducer*	0 [0, 14]	0 [0, 13]	0 [0, 0]

*Rocket-Rolon *vs* Surgicraft-Copeland, Mann–Whitney-U = 25054 P<0·05.
*Hewlett-Packard *vs* Surgicraft-Copeland, Mann–Whitney-U = 24032, P<0·05.
Results are median (interquartile range) values.

transducer was used significantly least often in the Surgicraft-Copeland group.

Questionnaires completed at 10 days after delivery were returned by 647 (83%) women. Similar numbers in the three trial groups remembered the electrode attachment (90%); 44 (7%) described it as 'moderately uncomfortable' and 42 (6%) as 'severely uncomfortable'. Fewer women who had been allocated to the Rocket-Rolon group found monitoring reassuring (61% *vs* 66% in the Hewlett-Packard group, and 67% in the Surgicraft-Copeland) and fewer would 'definitely have a fetal scalp electrode again' (43% *vs* 49% and 51%, respectively); but these differences were not statistically significant.

Discussion

This study was initiated following our observation that fetal scalp electrodes frequently needed to be replaced. This had raised concerns about the quality of continuous fetal heart rate monitoring in the hospital, about use of midwives' time to replace electrodes, and about possible adverse effects on the baby.

We believe that we have addressed these concerns reliably. We ensured before the study that those responsible for intrapartum monitoring were trained to use each of the electrodes interchangeably. Random allocation generated groups that were comparable in important respects (Table 1); compliance with the allocated electrode was satisfactory; those applying the electrodes were of similar status; and the application presented similar difficulties as judged by the position and dilatation of the cervix and the station of the fetal head (Table 2). Furthermore, the trial was sufficiently large to ensure identification of clinically important differences between the electrodes, and outcome was assessed 'blind' to the allocation, where possible.

We identified clear differences between the electrodes in respect of the need for replacement: this applied to 38% of those allocated to the Rocket-Rolon compared with 30% allocated to the Hewlett-Packard and 20% allocated to the Surgicraft-Copeland electrode. This was reflected in differences in the total number of replacements (Table 3), and in the number of electrodes that remained attached up to (or nearly up to) delivery (Table 3). The reason why the Hewlett-Packard performed better than the Rocket-Rolon was that it was less likely to require replacement because of a poor quality or absent trace. The Hewlett-Packard was also better than the Surgicraft-Copeland in this respect but this advantage was more than offset by the fewer replacements of the Surgicraft-Copeland because the electrode had become detached (Table 3). These differences between the electrodes persisted at later attachments.

The differences were also reflected in the type and quality of fetal heart rate monitoring. The Hewlett-Packard tended to produce more good quality traces compared with the Surgicraft-Copeland; nevertheless, the total time with an interpretable trace ('good' or 'adequate' quality) was similar in the groups (Table 5). Resort to monitoring with an abdominal transducer was least common in the Surgicraft-Copeland group.

There have been reports of serious neonatal complications of fetal scalp electrodes (Overturf & Balfour 1975; Plavidal & Werch 1976; Okado & Chow 1977; D'Souza *et al.* 1982; Cordero *et al.* 1983). In this trial, however, there was no serious scalp trauma, and bleeding from the scalp after delivery was equally common in the three groups (Table 3). The only advantage for the Rocket-Rolon identified in the trial was that it was least likely to leave a mark on the scalp that was still visible 10 days after delivery.

The purchase price (1990) of each electrode is as follows: Rocket-Rolon £3.65; Hewlett-Packard £4.42; and Surgicraft-Copeland £4.00. Taking into account the difference in the need for reapplications, the average costs of electrodes per woman, as allocated, were £5.55, £6.01 and £5.03, respectively. This calculation does not take account of other differences in direct costs, such as those incurred in vaginal examinations (about 20 fewer per 100 women monitored using the Surgicraft-Copeland), and possibly in caesarean or instrumental deliveries.

The trial has demonstrated clinically important differences between the performance of the three electrodes. The findings are consistent with the results of previously reported small trials (Calvert & Newcombe 1980; Nickelsen *et al.* 1989). The Surgicraft-Copeland was significantly least likely to become detached. This led to fewer vaginal examinations to apply a new electrode. In this respect, it was clearly preferable to the Hewlett-Packard and Rocket-Rolon both to clinical care givers and to the women.

On the basis of the results of this trial, we feel that the Surgicraft-Copeland is the electrode of choice.

Acknowledgments

We thank the many midwives and obstetricians in the West Berkshire Health District who worked so hard to make this study a success; the mothers who responded so enthusiastically to requests for information about their views; Pamela Dean for clerical assistance, Carole Harris for data entry, and Pauline Carter for typing the manuscript. Funding for this study was obtained through the locally organized research scheme (Oxford Region). The National Perinatal Epidemiology Unit is funded by a grant from the Department of Health.

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Received 26 April 1991
Accepted 25 October 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 307–309

FETAL AND NEONATAL MEDICINE

Fetal scalp and umbilical artery blood lactate measured with a new test strip method

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ABSTRACT

Objective To compare the measurement of lactate in fetal scalp and umbilical artery blood by a new dry reagent strip method with a commercially available enzymatic method using plasma (Monotest).

Design Comparative study.

Subjects Fetal scalp blood samples were obtained during labour from 24 fetuses and umbilical artery blood samples were obtained at birth in a further 51 deliveries.

Results The concentration of lactate in scalp and umbilical artery blood measured by the reagent strip method correlated well ($r = 0{\cdot}94$, $P<0{\cdot}001$ and $0{\cdot}95$, $P<0{\cdot}001$ respectively) with the enzymatic plasma method. The paper strip method tended to give lower readings than the enzymatic method when the fetal haematocrit was $\geqslant 50\%$.

Conclusions The new dry reagent strip method which takes only 1 min to carry out and requires only 20 µl of blood seems to be handy and reliable. This system provides a convenient and rapid test for measuring fetal blood lactate.

Fetal acidosis may be due to hypercapnia with or without lacticaemia. It has been postulated that hypercapnia is more acute, transitory and of earlier onset than lacticaemia, which is thought to result from a more long lasting hypoxia, to develop more slowly, to last longer and to be more harmful to the fetus. Most clinicians, when investigating fetal acid-base balance, have determined the scalp pH, which reflects hypercapnia as well as lactacidosis (Saling 1966). Since transient hypercapnia is rather common during normal labour (Ingemarsson & Arulkumaran 1986), fetal lactate concentration may be a more specific variable for assessing the condition of the fetus.

Cord blood lactate concentrations have been studied extensively (Eastman & McLane 1931; Räihä 1963; Rooth & Nilsson 1964) but only limited information is available about fetal scalp lactate values (Monti *et al.* 1968; Jacobson 1970; Yashiaka *et al.* 1970; Smith 1982; Schmidt 1988). The reason for this is that available techniques for estimating lactate have required rather large amounts of blood and have been time consuming, making fetal scalp blood sampling marginally practicable and not clinically useful.

In the present study we assessed a new and simple dry reagent strip method for measuring lactate in fetal whole blood (Shimojo *et al.* 1989). The method takes only 1 min and requires only 20 µl of blood. The simplicity of the method suggested that it could be a suitable tool for investigating fetal well-being.

Subjects and methods

Fetal scalp blood samples were randomly collected in 24 women in labour at a cervical dilatation of 6–10 cm. All the women were in a left lateral recumbent position during the procedure. Preheparinized glass capillaries were used to collect two blood samples of 100 µl each for the enzyme test and one sample of 20 µl for the strip test, which was performed immediately in the labour room.

Similar sets of three blood samples were collected from the umbilical artery in a further 51 deliveries, 50 were obtained immediately after birth (before the first cry) and one was collected from a clamped cord 15 min after delivery by emergency caesarean section for fetal asphyxia. Haematocrit was determined in 46 of the 51 cord artery blood samples.

Lactate determination

The paper strip method. The fetal blood (20 µl) was dropped on the filter paper of the test strip. The reaction principles are shown in Fig. 1. The concentration of lactate in the sample is stoichiometrically related to the intensity of the colour that develops 60 s after application of the blood sample. The concentration is read using a reflectometer (absorbance at 555 nm) calibrated with a standard strip.

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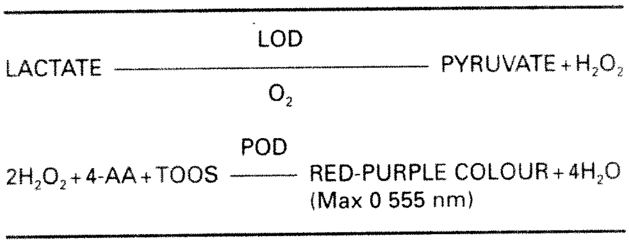

$$\text{LACTATE} \xrightarrow[O_2]{\text{LOD}} \text{PYRUVATE} + H_2O_2$$

$$2H_2O_2 + 4\text{-AA} + \text{TOOS} \xrightarrow{\text{POD}} \text{RED-PURPLE COLOUR} + 4H_2O \ (\text{Max } 0\ 555\ \text{nm})$$

Fig. 1. Reaction principles for estimating lactate concentrations in whole blood using a dry reagent paper strip method. Abbreviations: LOD = lactate oxidase; 4-AA = 4-amino-antipyrine; TOOS = N-ethyl-N-(2-hydroxy-3-sulfopropyl)-m-toluidine; POD = peroxidase.

Enzymatic method. The two 100 μl blood samples were combined and immediately transferred to a tube containing sodium fluoride to inhibit lactate production. The tube was then placed in a high speed centrifuge to separate plasma for the analysis. The lactate concentration was measured using a commercially available enzymatic method (Monotest: Boeringer Mannheim, Germany).

As the lactate values were not normally distributed, we used a FORTRAN program for ranking and for calculation of Spearman's correlation coefficient (Kempi 1985).

The project was approved by the local ethics committee.

Results

Lactate concentrations in fetal scalp blood ranged between 1·1 and 6·1 mmol/l when estimated with the paper strip method and between 1·4 and 6·4 mmol/l with the plasma enzymatic method. In umbilical artery blood the lactate values were estimated to range between 2·0 and >12·0 mmol/l (the upper limit of the calibration nomogram) with the paper strip method and between 1·5 and 14·5 mmol/l with the plasma enzymatic method. There was good correlation between the results obtained by the two methods: $Rs = 0{\cdot}94$, $P<0{\cdot}001$ for scalp blood values (Fig. 2); and $Rs = 0{\cdot}95$, $P<0{\cdot}001$ for cord blood values (Fig. 3) (Spearman's). Figure 4 demonstrates the difference in lactate concentration between the two methods in relation to the haematocrit in the umbilical artery blood (45 results are plotted, one lactate value exceeded the nomogram and was excluded).

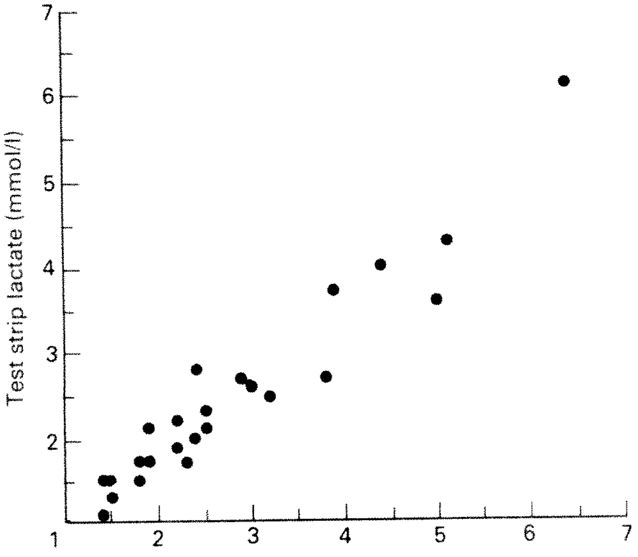

Fig. 2. Lactate concentrations in fetal scalp blood estimated by the dry reagent paper strip method in relation to the plasma enzymatic method.

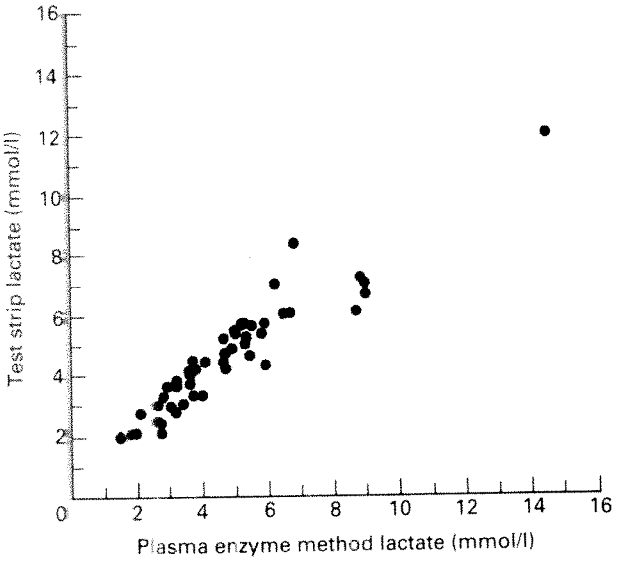

Fig. 3. Lactate concentrations in umbilical artery blood estimated by the dry reagent paper strip method in relation to the plasma enzymatic method.

Discussion

This study demonstrates clearly that the dry reagent strip system is a reliable tool for measuring fetal lactate concentrations. It fulfils several clinical practical requirements. It is rapid, simple and requires only a small amount of blood. Previous methods for lactate determination have required at least 150 μl of blood, which could be difficult to obtain from the fetal scalp. Consequently such methods have been used only for research purposes and have not been introduced into routine clinical practice. It seems that the new paper strip method could solve this problem. However, the clinical value of determining this variable remains to be established.

The present study indicated that the paper strip method was

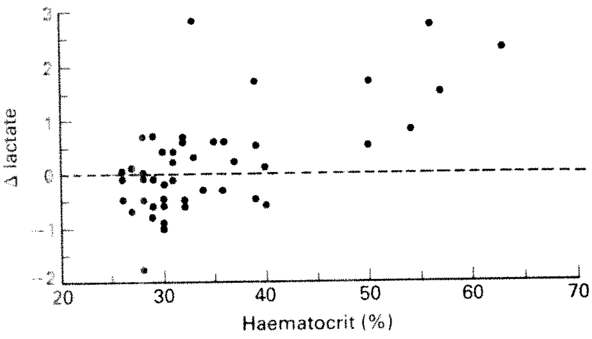

Fig. 4. The difference in umbilical artery blood lactate values between the two methods of measurement in relation to haematocrit concentration.

accurate within a range of cord blood haematocrit values between 26 and 49%. It is desirable that the accuracy is investigated further in samples with higher haematocrit concentrations, where it is possible that a slow diffusion into the reagent layer may result in false low values. In this study there were six cord blood haematocrit values of ⩾50%. In five of these, the paper strip method showed lactate values that were 0·5–2·3 mmol/l lower than with the plasma enzyme method, the sixth sample showed the highest lactate concentration, 14·5 mmol/l, with the plasma analysis. The nomogram for the lactate concentrations determined with the paper strip method ends at 12·0 mmol/l, and in this sample the value was higher. This factor may influence lactate assessment in polycythaemic, hypoxic fetuses and we are continuing to measure the lactate concentration in such cases by both methods.

Fetal blood lactate measurements have not been proven to be better than pH in predicting fetal condition. Smith (1982), in an extensive review and in a study of 310 labours, concluded that both pH and lactate values seem to be equally good in predicting fetal depression at birth. However, previous studies included only a small number of fetuses with asphyxia, making the comparison unsatisfactory. With the new paper strip method for lactate determination, it will be easier to obtain sufficient data to allow an accurate comparison between the two methods.

The potential value of measuring fetal lactic concentration has been convincingly demonstrated in animal experiments (Myers *et al.* 1981). The new technique offers the possibility of further elucidating these complex relations in the human fetus. The present study indicate that this new technique is handy and reliable. Only a small amount of blood is required and the result is available within 1 min. It is too early to state if this method will replace pH analyses or if it could be used as part of a 'biochemical Apgar score'. More information about the predictive value in relation to birth asphyxia and neonatal outcome is necessary to clarify its clinical usefulness. Such studies are in progress.

Acknowledgments

We should like to express our sincere gratitude to the Hisashi Sakamoto, Kyoto Daiichi Kagaku Co. Ltd., for technical help and making the study possible.

We also wish to thank Dr H. Östergaard and his staff at the Department of Biochemistry, County Hospital of Östersund, for kind help with analyses, and the labour suite staff for assisting the fetal scalp blood sampling.

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Received 10 January 1991
Accepted 15 September 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 310–313

GYNAECOLOGY

Perineal video-ultrasonography in the assessment of vaginal prolapse: early observations

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ABSTRACT

Objective To investigate the efficacy of perineal ultrasonography in the assessment of vaginal prolapse.
Design A prospective descriptive study.
Setting Urodynamic Unit, St. George's Hospital, London.
Subjects Six women, three of them were awaiting colposuspension and three had had a colposuspension.
Interventions Perineal ultrasound scans were performed on women with and without incontinence and prolapse, both before and after continence surgery. Movement of the bladder, urethra, uterus, vaginal vault and enterocele were observed during coughing and the valsalva manoeuvre.
Main outcome measures To assess reproducibility, six patients had six different measurements taken of bladder neck and prolapse position and movement relative to the symphysis. The measurements were plotted upon an X-Y co-ordinate axis. Each measurement was repeated three times and one way analysis of variance performed upon the readings.
Results Perineal ultrasonography clearly demonstrated movement of the whole pelvic floor. Minor degrees of both anterior and posterior vaginal wall prolapse could be seen and quantified. An increase in posterior vaginal wall mobility was noted in women after colposuspension. All measurements taken were found to be reproducible.
Conclusions Perineal ultrasonography is easy to perform and is reproducible. It may improve understanding of why some women develop posterior vaginal wall prolapse after colposuspension and, conversely, why some women develop incontinence following anterior repair for prolapse.

Ultrasound scanning techniques for the assessment of incontinence are becoming more widely used in gynaecology (White *et al.* 1980; Quinn *et al.* 1988), but these techniques have not been used to investigate prolapse, although in many cases the two are closely related. We have developed perineal video-ultrasonography to observe pelvic floor movement in continent and incontinent women with and without prolapse. As a research tool perineal ultrasound may improve understanding of why some women develop posterior vaginal wall prolapse following colposuspension, requiring a subsequent posterior repair, and why some continent women who undergo prolapse surgery, develop genuine stress incontinence postoperatively. This method may identify these women and improve their surgical management.

Subjects and methods

Perineal ultrasonography was performed using a 3·5 MHz linear array scanner (Siemens Sonoline SL–1). The patient was placed in lithotomy position and sat as upright as possible. A Foley catheter was inserted to identify the bladder neck and the bladder was filled with 250 ml of sterile saline. A rectal transducer was inserted to measure increases in intra-abdominal pressure on coughing and straining. An ultrasound probe covered with acoustic gel was placed on the perineum so as to give a sagittal view through the pelvis. The symphysis was easily seen as two bright parallel echoes. The Foley balloon was easily identified and the bladder neck corresponded to the junction of the balloon and the catheter.

The patient was initially assessed at rest. Measurements of distance from the bladder neck to the anterior, inferior border of the symphysis can be taken. The probe was then held in place on the perineum while the patient was asked to perform a valsalva manoeuvre, to cough once and then six times. During this sequence of events, movement of the pelvic floor and, particularly, the presence of prolapse was obvious. Descent of the bladder, urethra, uterus, vaginal vault and the development of an enterocele during coughing and the valsalva manoeuvre were noted. The scan obtained at maximum pressure during the valsalva manoeuvre was frozen for comparison with the frozen image from the resting position. Reproducibility within patients was determined by one observer (S.M.C.) repeating

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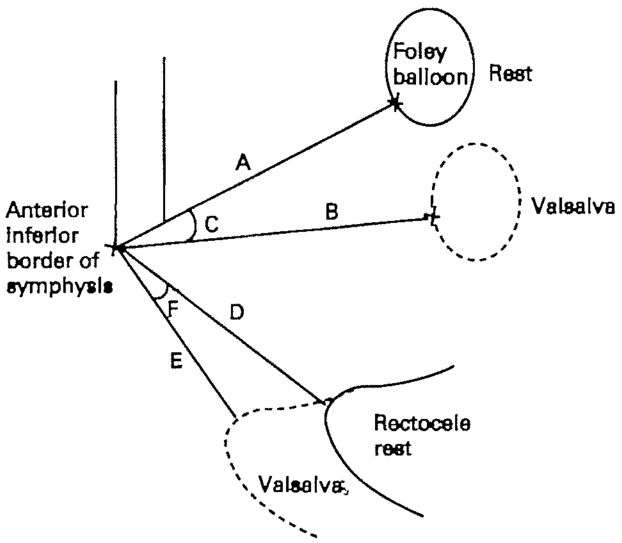

Fig. 1. Ultrasound measurements taken for the reproducibility studies. (A) Distance from the anterior, inferior border of the pubic symphysis to the bladder neck at rest; (B) The same distance at maximum pressure during the valsalva manoeuvre; (C) Angle of movement of the bladder neck during the valsalva manoeuvre; (D) Distance from the anterior, inferior border of the symphysis to the lowest point of the perineum (or rectocele) at rest; (E) The same distance during the valsalva manoeuvre; (F) Angle of movement of the lowest part of the perineum (or rectocele) during the valsalva manoeuvre.

the entire procedure three times, taking images for measurement at rest and at the point of maximum movement during the valsalva manoeuvre.

The purpose of the rectal transducer was to assess perineal movement at a standard pressure during the valsalva manoeuvre and to enable us to relate ultrasound observation in a patient to a standard pressure and also to allow comparison between patients. This whole sequence of cough and valsalva manoeuvre was recorded on video tape for later analysis.

Measurements

The anterior border of the pubic symphysis and its most inferior edge as observed on ultrasound were used as standard reference points. Movement of the pelvic floor relative to the anterior inferior border of the symphysis was observed, and distances between the bladder neck and symphysis were plotted and measured using the co-ordinate technique described by Clark *et al.* (1989).

Reproducibility

To assess the reproducibility of the technique, the following measurements were made (Fig. 1). The distance from the anterior inferior border of the symphysis to the bladder neck at rest (distance A) and again at maximum pressure during the valsalva manoeuvre (distance B) were measured three times in six patients. The angle of movement in degrees on moving from the rest position was also measured (angle C). The distance from the anterior inferior border of the symphysis to the lowest point of the perineum was also measured at rest (distance D) and again during the valsalva manoeuvre (distance E). Again the angle of movement from the rest position was measured (angle E). These measurements were made by the same observer taking six frozen images from each patient (three resting and three during the valsalva manoeuvre). These measurements were taken from the scan pictures by superimposing an X-Y grid over the scan as described by Clark *et al.* (1989). The measurements are given in Table 1.

Results

Pelvic floor movement

Video-ultrasonography clearly demonstrates movement of the whole pelvic floor and allows assessment of the close anatomical and functional relation of the pelvic organs. The pelvic floor moves on a pivot around the anterior, inferior border of the symphysis, with the bladder neck, bladder and posterior perineum moving downwards and forwards on increasing intra-abdominal pressure. This movement is seen to some degree in all women but is much more marked in women with prolapse and/or stress incontinence.

Movement of the anterior pelvic structures

Bladder neck displacement during coughing and the valsalva manoeuvre is clearly seen and can be quantified by measuring the change in angle and distance travelled (Clark *et al.* 1989). The presence of varying degrees of cystocele can be seen even if this is asymptomatic. A high cystocele has long been

Table 1. Measurements of bladder neck and prolapse position and movement during the valsalva manoeuvre relative to the symphysis

Patient No.	A (mm)	B (mm)	C (degrees)	D (mm)	E (mm)	F (degrees)
1	25	23	16	24	29	35
	25	22	15	25	29	40
	26	22	14	25	27	38
2	25	18	62	30	38	21
	23	16	48	28	36	19
	23	17	50	28	36	18
3	29	25	16	29	28	28
	28	24	12	26	28	30
	29	26	12	27	29	29
4	28	25	4	30	30	35
	28	25	7	28	26	36
	28	25	4	29	26	39
5	32	37	10	30	34	74
	32	35	9	31	32	70
	33	29	4	32	34	75
6	25	24	9	28	28	9
	25	24	4	29	30	13
	25	25	3	27	28	8

(A) Distance from bladder neck to anterior, inferior border of the symphysis at rest; (B) The same distance at maximum pressure during the valsalva manoeuvre; (C) Angle moved by the bladder neck around the symphysis during the valsalva manoeuvre; (D) Distance from the lowest point of the rectocele to the anterior, inferior border of the symphysis at rest; (E) The same distance during the valsalva manoeuvre; (F) Angle moved by the rectocele around the symphysis during the valsalva manoeuvre.

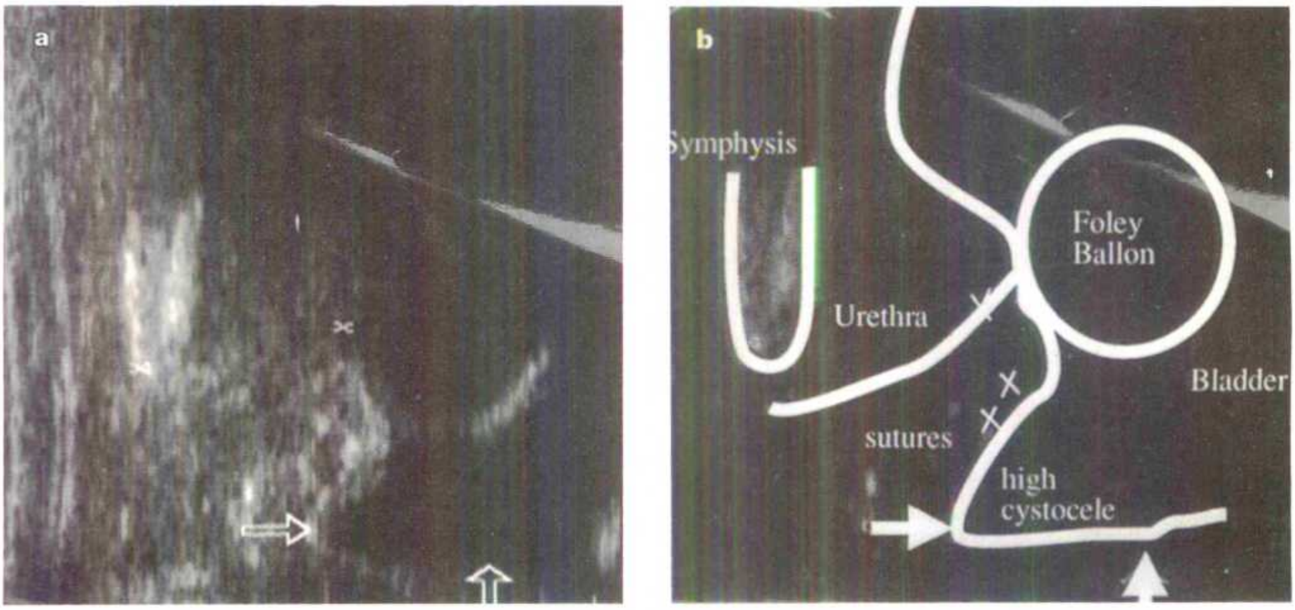

Fig. 2. (a): Perineal ultrasound scan of a high cystocele after colposuspension. The symphysis is seen as two bright parallel echoes and the bladder neck is taken as the point where the Foley balloon joins the catheter. Two arrows indicate the border of the cystocele. (b) Diagram showing the bladder, symphysis and Foley balloon outlined in white and the probable position of the colposuspension sutures marked with crosses. Two arrows indicate the border of the cystocele.

described as a finding in some patients after colposuspension and is usually asymptomatic. Fig. 2 shows a well-elevated bladder neck following colposuspension but a clearly defined large high cystocele.

Movement of the posterior vaginal wall

Video-ultrasonography shows that some degree of downward and forward posterior pelvic floor rotation occurs in most women but that this varies in amount. A rectocele can be seen as an area of brighter echo in the posterior pelvic floor and Fig. 3 shows a rectocele in a patient at rest. After successful colposuspension, movement of the posterior pelvic floor is much more marked. Video-ultrasonography shows that during coughing and the valsalva manoeuvre, the bladder neck is elevated and immobile, remaining in the same position in relation to the symphysis. The posterior vaginal wall is, however, considerably more mobile. Dynamic video studies demonstrate

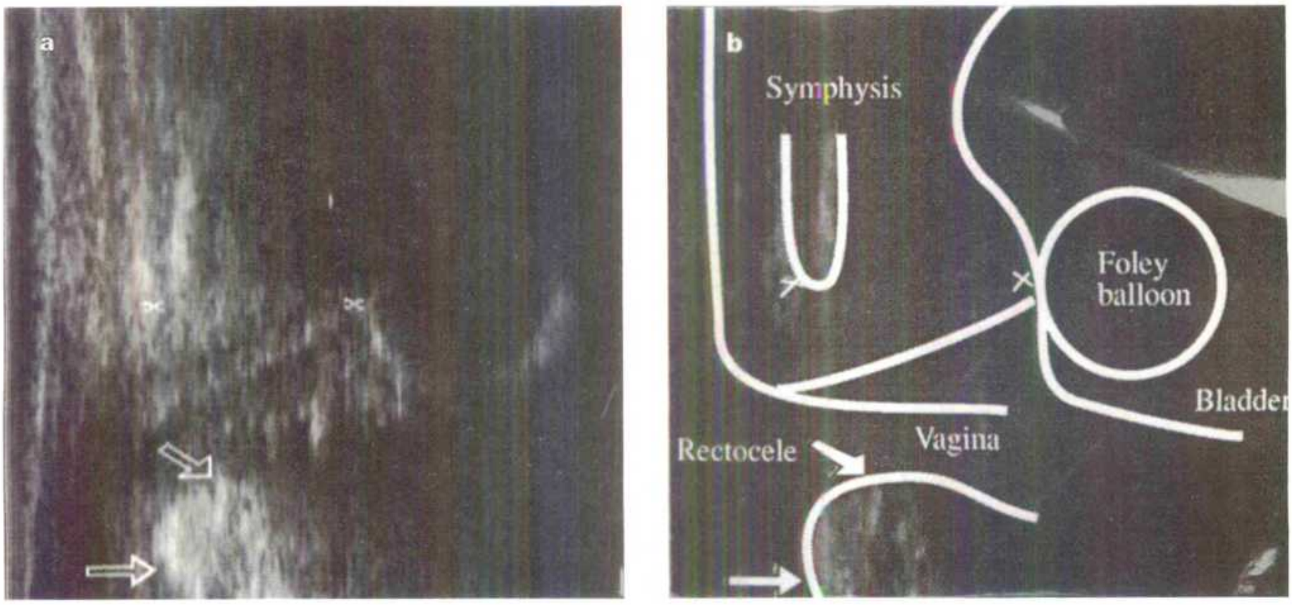

Fig. 3. (a) Perineal ultrasound scan of a rectocele at rest. The anterior inferior border of the symphysis and the Foley balloon are marked with crosses. Two arrows indicate the limits of the rectocele. (b) Diagram showing the symphysis, Foley balloon, bladder and vagina outlined in white.

forward rotational movement and in some patients the rectocele appears to be compressing the lower urethra on raising intra-abdominal pressure.

Reproducibility

One way analysis of variance was performed on each set of three readings of all six measurements taken (A, B, C, D, E, and F) for all six patients and confirmed the measurements to be reproducible. There was no significant difference between the three readings taken at each point and Bartlett's test of variance was non-significant ($P>0{\cdot}05$) for all groups. Of the six women whose ultrasound measurements are given in Table 1, patients 1, 2 and 3 were awaiting colposuspension and patients 4, 5 and 6 had had colposuspensions. Patients 1 and 2 each had a small cystocele and patient 3 had a moderate cystocele. None of these three had posterior vaginal wall prolapse. Patients 4, 5 and 6 had no anterior vaginal wall prolapse but patient 5 had a moderate rectocele. It can be seen that the amount of movement measured in millimeters correlates directly with the degree of prolapse detected on clinical examination.

Discussion

The perineal probe is very suitable for the assessment of prolapse. It is comfortable for the patient and a good view of symphysis and bladder neck can be obtained. Its main advantage is that it can be held on the perineum during coughing and the valsalva manoeuvre so that the whole movement can be watched. Both the rectal and vaginal probes are difficult to keep in place during raised intra-abdominal pressure and a large prolapse may even push such a probe out.

Our demonstration of posterior wall movement would explain the observations of Hilton (1981) of greater than 100% pressure transmission to the urethra, on raising intra-abdominal pressure following colposuspension. Hertogs & Stanton (1985) placed a vaginal barrier to prevent urethral compression by a high cystocele and found a transient recurrence of incontinence. Our video studies demonstrate that pressure transmitted through the rectum and posterior vaginal wall may also exert urethral compression.

It is more difficult to quantify movement of the perineum and of posterior vaginal wall prolapse and we are currently assessing ways of adapting the X-Y co-ordinate system to obtain objective measurements of the size and mobility of prolapse. A large prospective trial could then be made to assess the effects of prolapse and continence surgery upon the dynamics of the pelvic floor.

Perineal uro-ultrasonography is an exciting new technique in the study of pelvic floor function and prolapse. The present study demonstrates it to be accurate and reproducible. Further assessment of these initial observations is necessary but video-ultrasonography can contribute to our understanding of the function of the female pelvic floor and the development of prolapse.

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Received 30 April 1990
Resubmitted 12 February 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 314–318

GYNAECOLOGY

A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN)—a preliminary report

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ABSTRACT

Objective To assess the efficacy of cervical conization as primary management of cervical intraepithelial glandular neoplasia (CIGN).

Design A multicentre prospective cohort study.

Setting CRC Clinical Trials Unit, Birmingham.

Subjects 84 women registered with the Unit between May 1986 and January 1989. After excluding 33 women, 51 who had been managed in accordance with the described protocol and had the presence of CIGN confirmed by central review of diagnostic histopathological material were included in the study.

Intervention/Protocol Women with CIGN diagnosed on a cervical cone specimen were managed in accordance with a specific protocol: (a) women with negative cone margins were managed conservatively and followed up with regular cervical cytological and colposcopic examinations; (b) women with involved cone margins were managed by hysterectomy.

Main outcome measures Presence or absence of CIGN at cone margins, results of cervical cytological examinations following conization, results of histopathological assessment of any surgical specimens taken after initial cone biopsy.

Results Of the 51 women with confirmed CIGN, managed by conization, 14 (27%) were aged 30 or less and 15 (29%) were nulliparous. Thirty five women who had a cone biopsy showing margins free of CIGN have been managed by conization alone. After a median follow-up period of 12 months there is no apparent residual CIGN or invasive disease in this group. Thirteen women have had further surgical procedures (according to protocol) and two have had a hysterectomy for benign gynaecological disorders. Eight further procedures were carried out because the original cone biopsy had margins involved with CIGN, and only one of them was found to have residual CIGN. The other five procedures were carried out solely because of abnormal cytology, only one of them had a diagnosis of CIN 1. A total of 10 women had cytological abnormality following cone biopsy, one had CIGN, one had CIN 1 and a third had CIN 3.

Conclusions Our preliminary data suggests that when a diagnosis of CIGN is made upon a cone biopsy, further surgery is unnecessary in those women in whom the margins of the cone specimen are free of disease. Cytological and colposcopic follow up, including cytological sampling of the endocervical canal, is recommended for these women.

Cervical intraepthelial glandular neoplasia (CIGN) is an uncommon lesion with uncertain incidence, aetiology and natural history. It comprises cervical glandular atypia (Brown & Wells 1986) and adenocarcinoma in situ (AIS). The management of this lesion is contentious and clinical opinion has been influenced by the results of small retrospective clinico-pathological studies. These studies have usually advocated hysterectomy as definitive management (Weisbrot *et al.* 1972;

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Qizilbash 1975; Christopherson *et al.* 1979; Hopkins *et al.* 1988). A growing body of opinion suggests that cone biopsy may be sufficient treatment provided the margins of the specimen pass through normal tissue (Ostor *et al.* 1984; Luesley *et al.* 1987; Bertrand *et al.* 1987; Andersen & Arffmann 1989). However, there has been no prospective assessment of management by cone biopsy and all the reports quoted involve small numbers. We describe a prospective cohort study to assess the efficacy of conization in the management of CIGN.

Subjects and methods

Women were included in the study if they had histologically proven CIGN, with or without an associated squamous component, in a cone biopsy specimen. They were considered ineligible for the study if they had concurrent atypical endometrial pathology, if there was concurrent benign gynaecological pathology that would normally necessitate hysterectomy, if there was evidence of invasive adenocarcinoma, or if it was unlikely that regular cytological follow-up could be guaranteed.

For those registered in the study, a request was made for representative histopathological material to be submitted for central independent pathology review. A questionnaire was sent to consultants registering patients in the study to ascertain the following information. (1) Cytological findings at the time of referral to hospital. (2) Colposcopic findings, including results of colposcopically directed biopsy. (3) Length of cone biopsy in millimetres from apex (endocervical margin) to base (ectocervical margin). (4) Status of excision margins of cone biopsy (free of disease or involved with disease). (5) Details of cytological and colposcopic follow-up examinations, and (6) details of any surgery after initial cone biopsy.

After enrolment in the study a questionnaire was sent to the clinicians and cytologists at 6-monthly intervals requesting information on the women's progress, particularly the result of the most recent cytological examination, and details of any further surgery.

Pathology review

Representative pathological material was submitted for central pathology review. This review was considered essential to verify the diagnosis of CIGN which is made infrequently in routine hospital practice, and can easily be confused with benign conditions of the endocervix, such as tubal metaplasia (Wells & Brown 1986). The review panel consisted of three pathologists with a special interest in gynaecological pathology (T.P.R., M.A. and C.H.B.).

Suitability for inclusion and confirmation of abnormality in subsequent specimens was dependent on central review. A standard proforma was completed by the histopathologist for each specimen examined. All of the patients described in this report had undergone review by at least one member of the panel.

Study protocol

Following registration in the study, further management was determined by the result of examination of the margins of excision of the cone specimen. This assessment was made by the pathologist at the referring institution who had access to all the diagnostic material. If the cone margins were free of CIGN, no further operative treatment was recommended, but regular cytological follow-up was advised. If the margins of excision were involved by CIGN it was recommended that hysterectomy or a second cone biopsy should be performed 4 months later. The choice of surgical procedure was left to the discretion of the referring gynaecologist and the 4-month interval was advised to allow time for the surgical inflammatory reaction to subside, theoretically enabling more accurate histopathological and cytological analysis. It was advised that further surgery should be preceded by one additional cytological assessment, allowing a comparison of the predictive accuracy of excision status and cytological assessment in determining the presence or absence of residual disease. The length of the cone specimen measured from the apex of the cone (the upper endocervical margin) to its base (the ectocervical margin) was recorded routinely.

It was advised that all the women should be followed up at 4-monthly intervals for 2 years and annually thereafter and that cytological samples be collected at each follow up visit using the endocervical cytobrush (Medscand), in addition to the standard Ayre's spatula. In all patients with persistently abnormal cytology, a request was made for further histological material to be obtained. However, the precise management in individual patients was left to the discretion of the referring clinician.

Consultants registering women in the study were asked to inform them that they were being managed in the context of a clinical trial. The study protocol stressed that informed consent should be obtained and the consultant registering the case was required to determine whether the local ethics committee required written consent.

Results

Four patients were excluded at the time of registration as they had not been managed in accordance with the study protocol. Insufficient clinical information was available on 15 women and central histopathological review led to exclusion of five others on the grounds that there was a suspicion of invasive disease (Table 1). Nine women were excluded because no CIGN was demonstrated in the cone specimen.

The data which follow relate to 51 patients in whom the diagnosis of CIGN was confirmed by central pathology review and invasive disease was excluded, follow-up cervical cytology was carried out after conization, and full information on management was received from the referring clinician.

The mean age of the 51 women was 35·7 years (range 19–56). The median parity was 1 (range 0–6). Fourteen women (27%) were aged 30 years or less when diagnosed and 15 (29%) were nulliparous. A breakdown of the grade of CIGN, age and parity is given in Table 2. The 51 women were recruited from 24 centres across the country.

Method of diagnosis of CIGN

In 27 women (53%), the cervical smear taken before diagnosis of CIGN was reported as showing atypical glandular cells and

Table 1. Subjects excluded after pathology review had indicated the likelihood of invasion

Subject	Original diagnosis	Reviewer 1	Reviewer 2	Reviewer 3
1	AIS	AIS Invasion in fragment	AIS Invasion in fragment	AIS only
2	AIS (+ CIN 3)	AIS + ?Invasion	AIS + ?Invasion	AIS only
3	AIS	AIS + Invasion	AIS + Invasion	AIS + Invasion
4	AIS	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
5	AIS	AIS + ?Invasion	AIS + ?Invasion	AIS only

Abbreviations: AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia.

in 13 of these there was also squamous cell dyskaryosis. Four women whose cervical smear showed atypical glandular cells had evidence of a glandular abnormality on a colposcopically directed biopsy.

Ten women (20%) had evidence of glandular abnormality on a colposcopically directed biopsy in the absence of previously suggestive cytological changes. The remaining 14 women (27%) had the diagnosis of CIGN made on cone biopsy in the absence of any cytological or punch biopsy forewarning of glandular abnormality. Whereas only about half the women with CIGN had cytology indicative of glandular abnormality, 89% of associated CIN lesions were accurately predicted by cytology ($\chi^2 = 7{\cdot}9$, $P < 0{\cdot}01$).

Follow-up and further management

(a) Margins of cone ciopsy free of CIGN

Of the 42 women in this category, 35 have had no further treatment since enrolment in the study. The other seven have had further surgery: in five the indication was abnormal cytology and the remaining two women had a hysterectomy for incidental benign gynaecological pathology. No residual disease was found in the cervices of the last two women.

Seven women had abnormal cytology following cone biopsy, and they have been managed as follows. Two have had no further surgery. One of them, whose original cone specimen showed AIS/high grade CIGN only, had a smear showing mildly dyskaryotic squamous cells 33 months after the original cone biopsy. Colposcopy showed a small wart like area on the posterior lip of the cervix which was biopsied and showed CIN 3. She was offered hysterectomy but declined any treatment. The other woman who has not had further surgery had a smear showing borderline changes 18 months after cone biopsy. Colposcopic examination was normal and it was decided that unless this minor degree of cytological abnormality persists, cytologic and colposcopic follow up will be continued. Five of the women with abnormal cytology after cone biopsy have had additional surgical procedures. Of these, two had a hysterectomy at 18 and 33 months, respectively, after cone biopsy because of persisting borderline cytological abnormalities but no residual CIGN or CIN was found in the cervix in either of the women. The other three women had a second cone biopsy: one of them had CIN 1 and the other two had no residual disease.

Table 2. Characteristics of 51 women with cervical intraepithelial glandular neoplasia (CIGN)

Variable	Number	Mean age	Median parity
Degree of CIGN			
Mild/moderate	6	34·3	2
Severe/AIS	45	36·4	1
Association with CIN			
Pure CIGN	25	37·7*	2
CIGN + CIN	26	32.9	1

There were no significant differences in parity (Mann Whitney *U*-test) between the groups. The women with pure CIGN were significantly older than those with CIGN + CIN *$P < 0{\cdot}05$, Student's *t*-test.
AIS = adenocarcinoma in situ, CIN = cervical intraepithelial neoplasia.

The median duration of follow up for this group was 12 months (range 4–39) and the median number of follow-up smears was 2 (range 1–10).

(b) Margins of cone biopsy involved with CIGN

All eight women in whom the margins of the diagnostic cone biopsy were involved with CIGN were managed by hysterectomy. Only one was found to have residual CIGN. This woman had a cervical smear before hysterectomy which suggested the presence of glandular cell abnormality.

(c) Indeterminate cone margins

In one woman it was impossible to assess the status of the margins because of extensive laser artefact. This woman has had three negative smears since conization, the last smear having been taken 15 months after diagnosis of CIGN.

Relation between follow-up cytology and status of excision margins

In one instance it was not possible to assess the status of the cone excision margins and three women who had margins involved with CIGN on cone biopsy did not have a further cyt-

Table 3. Relation between follow up cytology and status of excision margins for cervical intraepithelial glandular neoplasia (CIGN) on cone biopsy ($n = 47$)

	No.	Abnormal cytology	Negative cytology
Involved margins	5	3 (60%)	2 (40%)
Free margins	42	7 (17%)	35 (83%)

χ^2 with Yates' correction = 2·76 n.s.

Table 4. Relation between follow up cytology and length of cone specimen ($n = 44$)

Cone length (mm)	*n*	Abnormal cytology	Negative cytology
< 25	29	8 (28%)	21 (72%)
≥ 25	15	1 (7%)	14 (93%)

χ^2 with Yates' correction = 1·53 n.s.

ological assessment before hysterectomy. The relation between follow-up cytology and status of excision margins was analysed in the remaining 47 women (Table 3).

Three of the five women with involved margins had abnormal cytology after the cone biopsy. One had a smear showing moderate squamous dyskaryosis with some features suggestive of glandular cell abnormality; no residual disease was found in the cervix after hysterectomy. Another had a smear suggestive of glandular atypia and was found to have residual CIGN in the hysterectomy specimen. The third woman, who had a smear showing borderline abnormalities, had no residual cervical disease.

Relation between follow-up cytology and length of diagnostic cone biopsy

In four women the length of the cone biopsy was not recorded and three women did not have a follow up smear taken after conization and before hysterectomy. The relation between follow-up cytology and the length of the diagnostic cone biopsy was examined in the remaining 44 women (Table 4). A length of 25 mm was chosen to distinguish between long (≥ 25 mm) and short (< 25 mm) cones (Bertrand *et al.* 1987).

The mean cone length in those who developed abnormal cytology was 18·5 mm compared with a mean length of 22 mm in those with negative cytology. This difference was not statistically significant (Student's *t*-test).

Relation between cone biopsy length and status of excision margins

In one case it was not possible to assess the status of the cone excision margins and in four cases the cone biopsy length was not recorded. The relation between cone biopsy length and status of excision margins was examined in 46 women (Table 5).

Discussion

This is the first prospective study to examine the efficacy of cone biopsy in the management of cervical intraepithelial glandular neoplasia. The data on cone length, status of excision margins and cytological follow-up provide some support for the view that conization may be sufficient *primary* management. In this study, 83% of women with margins free of CIGN on the initial cone biopsy had negative cytological follow-up afer a median follow up period of 12 months.

Abnormal cytology following initial treatment in 10 of 51 (20%) suggests that these women are at risk of residual CIGN ($n = 1$) or CIN ($n = 2$), therefore women managed by conization as primary therapy require careful cytological and colposcopic follow-up.

There was only one instance of a 'long' cone (≥ 25 mm) having involved excision margins and only one of the 16 women who had a long cone had abnormal cytology at follow up. Although the relation between the length of the cone and subsequent cytology was not statistically significant, our findings concur with the opinion of Bertrand *et al.* (1987) and Colgan & Lickrish (1990) that a cone biopsy of ≥ 25 mm should be successful in clearing the lesion.

Our experience so far suggests that abnormal cytology after conization is a more sensitive indicator of residual disease (3 of 10 women with abnormal smears had some residual pathology) than is the identification of positive cone margins (1 of 8 had residual pathology). However, the numbers are too small for firm conclusions to be drawn.

A significant difference was noted in the age of women with 'pure' glandular lesions compared with women with 'mixed' CIGN and CIN, the latter being, on average, 4·8 years younger. The explanation for this finding may be that the presence of CIN, which is efficiently detected by exfoliative cytology, facilitates the diagnosis of CIGN which is less readily recognized. Our study supports this hypothesis as CIGN was a chance finding on histological examination of a cone specimen in 27% of our study group where there was no forewarning of glandular abnormality on cytology, colposcopy or directed biopsy of the cervix.

Previous studies have indicated that glandular epithelial atypias of lesser degree than adenocarcinoma *in situ* occur in up to 15% of women who have CIN 3 (Brown & Wells 1986). Of these, 68% were believed to be 'low grade'. There have been no other reports of such a high prevalence of low grade glandular atypias and our finding of only 6 of 51 (12%) with low grade atypia (as defined by Brown & Wells 1986) suggests either that such atypias are infrequent, or that there is considerable subjectivity in grading between pathologists. This issue is being addressed by the pathology review panel who aim to assess the degree of agreement between observers in the grading of these lesions. Whereas we have noted a high level of agreement concerning the major diagnostic features of this lesion, it can be difficult to exclude early invasive disease with confidence in a minority of them. Five of 84 [6%] women registered in the study, whose pathology slides have been reviewed, had some evidence of early invasive disease and were therefore excluded; in two of them the diagnosis of invasion was neither certain nor unanimous. Other reports have recognized that the distinction between early invasive adenocarcinoma and AIS can be difficult (Brand *et al.* 1988). Our study was undertaken to assess the management of pre-invasive disease. A separate study is required to establish the optimum management for these difficult cases with suspected

Table 5. Relation between length of cone biopsy and status of cone margins for cervical intraepithelial glandular neoplasia (CIGN)

		Status of margins	
Cone length (mm)	*n*	Free	Involved
< 25	30	23 (77%)	7 (23%)
≥ 25	16	15 (94%)	1 (6%)

χ^2 with Yates' correction = 1·1 n.s.

early invasion, but it has been suggested that they follow a benign course (Teshima *et al.* 1985).

Our observations suggest that cytological detection is less efficient for CIGN than for CIN. How can this apparent lack of sensitivity for detection of glandular abnormalities in smears be reconciled with our use of cytologic examination as the mainstay of follow up? It is worthy of emphasis that, before diagnosis of the CIGN lesions in this study, routine cytologic sampling of the endocervical canal had not been employed. We recommended that follow-up cytological assessment of women with CIGN should consist of routine Ayre spatula sampling combined with a brush smear from the endocervical canal. The criteria for cytological identification of specific glandular lesions are less generally accepted than those for CIN. Undoubtedly, better definition and wider recognition of the criteria for cytological diagnosis of CIGN would improve the detection of these lesions and the anticipated results of our independent review of cytological diagnosis in these patients may be helpful.

When the cone margins have appeared to be free of disease, no residual CIGN or invasive disease has so far been encountered after using conization as definitive management in 42 women with confirmed CIGN studied prospectively. When conization has failed to yield a specimen with disease free margins, further surgery has been carried out. Although the conclusions from these observations are limited by the small numbers, the majority of women with positive margins for CIGN had no residual disease at hysterectomy and, more reassuringly, there was no instance of unsuspected invasive disease in the remaining cervix. In the only instance of residual moderate grade CIGN in a woman whose cone biopsy margins were involved with disease, cytology before hysterectomy showed atypical glandular cells. It can therefore be concluded that the application of our management protocol has been effective, but the observations clearly require confirmation by long term follow up.

Acknowledgments

We would like to thank all the clinicians and pathologists who have contributed material to this study and Mrs J. Hull and the late Mrs J. Sharp of the CRC Clinical Trials Unit, Queen Elizabeth Hospital, Birmingham for their assistance with registration of women in the study. We would also like to express our gratitude to the BSCCP (British Society for Colposcopy and Cervical Pathology) for its support in publicising this study among its members.

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Received 21 March 1991
Accepted 12 January 1992

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 319–324

GYNAECOLOGY

Endometrial responses in artificial cycles: a prospective, randomized study comparing three different progesterone dosages

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ABSTRACT

Objective To examine the endometrial response to three different regimens of progesterone.
Design A prospective, randomized study.
Setting The Jessop Hospital for Women, Sheffield.
Subjects 14 women with premature ovarian failure divided into two equal groups.
Interventions Three different regimens of hormone replacement therapy containing standard, high and low progesterone dosages. One group received the standard regimen in one cycle and high dosage regimen in another cycle. The second group received the standard regimen in one cycle and low dosage regimen in another cycle. The order of the two dosage regimens was randomized by lottery.
Main outcome measures Ultrasonographic measurement of endometrial thickness and morphological study of endometrial biopsy specimens taken on day 19 of the cycle using the traditional dating criteria and morphometric techniques.
Results Compared with standard regimen cycles, the endometrial response in cycles treated with the low dosage regimen showed significant retardation of overall endometrial development and changes in a number of morphometric measurements. The response of endometrial glands to the high dosage regimen was similar to that of the standard regimen, although the stromal cell diameter was increased.
Conclusions In women receiving hormone replacement therapy normal endometrial development depends on an adequate dosage of progesterone, but increased dosage above our standard regimen does not produce any further change in the glandular component of the endometrium.

It is generally accepted that normal endometrial development in the peri-implantation period is crucial for successful implantation. Abnormal endometrial development in the luteal phase is associated with unexplained infertility (Li *et al.* 1991) and a poor prognosis for subsequent pregnancy (Klentzeris *et al.* 1992). Normal endometrial development is dependent on normal amounts of steroid hormones, especially oestradiol and progesterone, produced by the ovary. In women with non-functioning ovaries, steroid hormones may be administered to produce an artificial cycle with normal endometrium capable of supporting implantation and pregnancy. A number of hormone replacement therapy (HRT) regimens have been reported to be successful in achieving this (Lutjen *et al.*1984; Navot *et al.* 1986; Rosenwaks, 1987; Serhal & Craft 1987; Asch *et al.* 1988; Droesch *et al.* 1988; Devroey *et al.* 1989; Steingold *et al.* 1989; Ben-Nun *et al.* 1989). One component of such regimens, progesterone, is indispensable in the normal development of the endometrium leading to implantation (Finn 1985) and the maintenance of early pregnancy (Csapo & Pulkkinen 1978). However, the optimal dosage of progesterone required to produce normal endometrial development is still not clear.

Devroey *et al.* (1989) have reported that normal endometrial maturity in the mid luteal phase (day 21) of the artificial cycle could be achieved with a wide range of serum progesterone concentrations (less than 10 ng/ml to over 30 ng/ml). Such variation may be due to several factors. For example, there can be significant variation in the response of a particular individual to steroid hormones (Fraser *et al.* 1989; Li *et al.* 1991) and the subjective nature of the histological assessment may lack precision (Li *et al.* 1989).

To overcome these problems, we have conducted a prospective, randomized study using morphometry, an objective and quantitative histological technique, to examine the endometrial response in artificial cycles produced by three different regimens of progesterone. By refining the measurement and dating criteria and giving the same subject a different dosage of progesterone in successive cycles, we have been able to eliminate many of the potential uncertainties in this type of experiment.

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Subjects and methods

The study involved 14 women with premature ovarian failure attending the gynaecological outpatient clinic at the Jessop Hospital for Women. Premature ovarian failure was defined as amenorrhoea for $\geqslant$6 months, associated with persistently low plasma oestradiol ($<$100 pmol/1) and elevated plasma follicle stimulating hormone (FSH) ($>$20 iu/1), in a woman $<$40 years of age (Mattison *et al.* 1984). All the women had blood tests for chromosomal analysis and anti-ovarian antibody.

The 14 women were divided into two equal groups at random. Each woman was treated with Cyclo-Progynova 2 mg (Schering, Sussex) in a pre-study cycle, followed by two study cycles in which one of the following three HRT regimens was administered (Table 1). (a) Standard regimen (Navot *et al.* 1986); (b) high progesterone regimen, in which the doses of progesterone were 5 times those of the standard regimen; (c) low progesterone regimen, in which the doses of progesterone were ⅕ those of the standard regimen.

The women in the first group were randomized by lottery to receive the standard regimen in one cycle and the high progesterone regimen in another cycle (high progesterone group). The women in the second group were randomized by lottery to receive the standard regimen in one cycle and the low progesterone regimen in another cycle (low progesterone group).

On day 19 of each study cycle, a 10 ml sample of blood was taken for assay of FSH, LH, oestradiol and progesterone. The endometrial and uterine thicknesses were measured by ultrasonography and an endometrial biopsy was obtained. In two women in the high-progesterone group, blood samples were not obtained because of poor access to peripheral veins as a result of previous chemotherapy.

Hormone assays

Progesterone was assayed by non-extraction, solid phase radioimmunoassay (RIA) using ^{125}I as a marker (Diagnostic Products Limited, Abingdon, Oxon). The sensitivity of the assay was 0·16 nmol/l and the mean intra- and inter-assay coefficients of variation were 7·2% and 7·9%, respectively.

Oestradiol was assayed by non-extraction, solid phase radioimmunoassay (RIA) using ^{125}I as a marker. The sensitivity of the assay was 29 pmol/l and the mean intra- and inter-assay coefficients of variation were 5·4% and 6·4%, respectively.

Table 1. Dosages of oestradiol valerate and progesterone in the three hormone replacement regimens.

Day of cycle	Oral oestradiol valerate (mg)	Intramuscular progesterone (mg)		
		Low progesterone regimen	Standard regimen	High progesterone regimen
1–5	1	—	—	—
6–9	2	—	—	—
10–13	6	—	—	—
14	2	—	—	—
15–16	2	5	25	125
17	2	10	50	250
18–26	4	10	50	250
27–28	1	5	25	125

LH was measured by immunoradiometric assay (IRMA), incorporating two high affinity monoclonal antibodies, using ^{125}I as a marker (Serono Diagnostics Limited, Surrey). The sensitivity of the assay was 0·15 IU/l. The mean intra- and inter-assay coefficients of variation were 5·0% and 5·5%, respectively.

FSH was measured by immunoradiometric assay (IRMA) incorporating two high affinity monoclonal antibodies, using ^{125}I as a marker. The sensitivity of the assay was 0·25 IU/l. The mean intra- and inter-assay coefficients of variation were 2.0% and 3.3%, respectively.

Ultrasonography

The maximum thicknesses of the uterus and endometrium, as seen on longitudinal section with a transabdominal real-time scanner (Combison 320, Kretztechnik, Zipf, Austria), were measured three times. The mean values obtained were used for subsequent calculation. The ultrasonography was performed by two observers, with an inter-observer coefficient of variation of about 8%. The endometrium was measured from the echogenic interface of the junction of the endometrium and myometrium and the result therefore represents the epthelial and stromal layers of endometrium.

Endometrial biopsy

Endometrial biopsies were obtained as an outpatient procedure using a Sharman's curette (Down Surgical Ltd, Sheffield, UK). A single endometrial specimen was obtained from the fundus and upper part of the body of the uterus. Each specimen was fixed immediately in 2% glutaraldehyde in cacodylate buffer (pH 7·4) for 4–6 h. It was then washed in buffer, dehydrated and embedded in JB-4 (Polysciences, Inc, Warrington, PA, USA), a plastic polymer. The specimen was sectioned at 2 µm and the sections were stained with acid fuchsin and toluidine blue for examination by light microscopy.

All the endometrial biopsies were dated histologically by two different methods: the traditional dating criteria (Noyes *et al.* 1950) and morphometry, the details of which have been described previously (Li *et al.* 1988; Dockery *et al.* 1990). The mean stromal cell diameter was measured using a digitizing tablet (Calcomp 'bit pad') linked to a microcomputer and the volume fraction of endometrium occupied by stromal cell nuclei was estimated by point counting (Weibel 1979).

Ethical aspects

Informed consent was obtained from each woman participating in the study. Approval for this study had been obtained from the ethics committee of the former Southern District of the Sheffield Health Authority.

Statistics

Comparison of results within women, treated as matched pairs, was performed by the Wilcoxon matched-pair non-parametric test. This was performed on the Statistical Package for Social Science (SPSS-X), available within the IBM mainframe computer of the University of Sheffield.

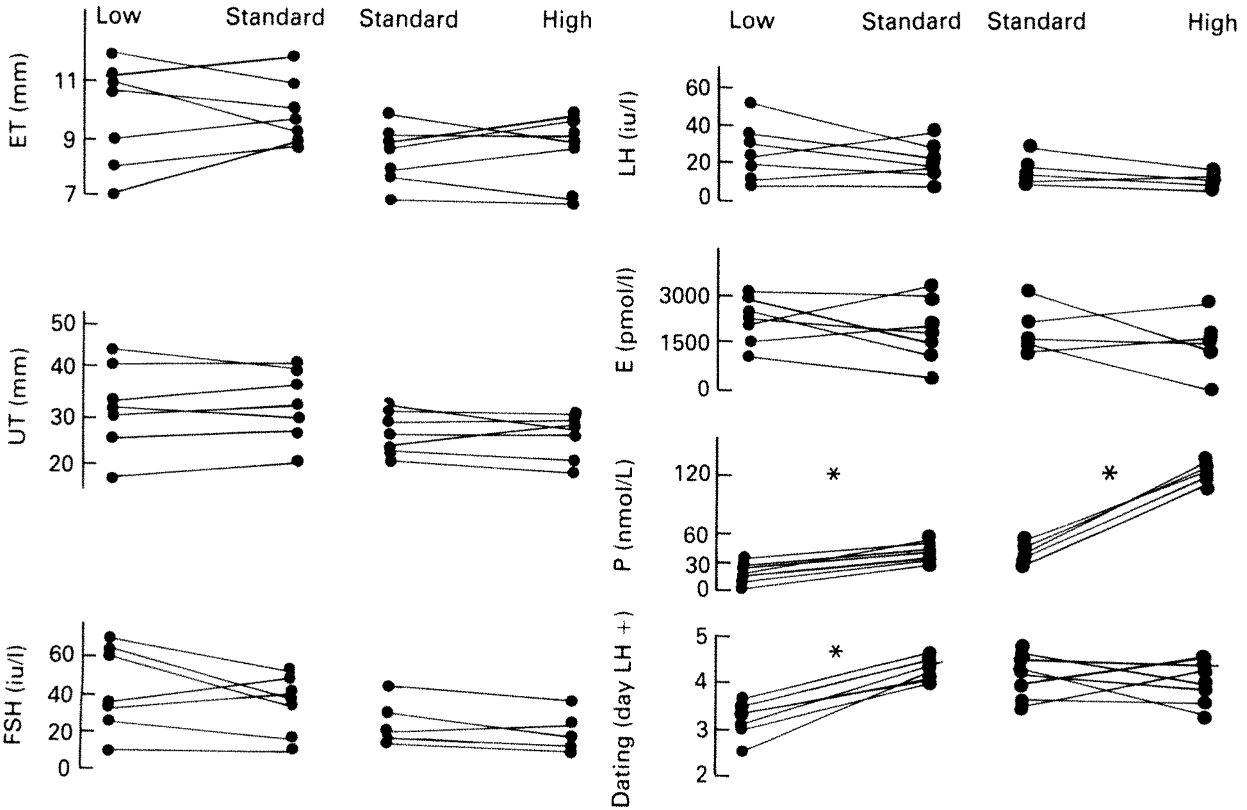

Fig. 1. Endometrial thickness (ET), uterine thickness (UT), plasma levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E) and progesterone (P), and histological dating of endometrial biopsy on day 19 of artificial cycles in two treatment groups. One group received the standard and high progesterone dosage regimens, whereas the second group received the standard and low progesterone dosage regimens. * significant difference between matched pairs ($P<0{\cdot}05$).

Results

Ten of the 14 women in the study had idiopathic premature ovarian failure, two had premature ovarian failure due to previous chemotherapy for lymphoma and two had Turner's syndrome. The mean age of the subjects was 31·0 (SD 3·4) years. The mean duration of premature ovarian failure, excluding those with Turner's syndrome, was 5·9 (SD 3·1) years.

In Fig. 1, the results of plasma FSH, LH, oestradiol and progesterone concentrations, ultrasonographic measurements and histological dating of the endometrial samples obtained on day 19 of the cycle are summarized. Women treated with standard dosage of progesterone had significantly more advanced histological dating results and higher plasma progesterone concentrations, than those treated with low dosage of progesterone. In contrast, women treated with high dosage of progesterone did not show any histological differences, although the plasma progesterone concentration results were higher, compared with those treated with the standard dosage of progesterone.

Typical examples of endometrial morphology produced by different hormone regimens are shown in Fig. 2. In one subject in the low progesterone group the endometrial morphology in the cycle treated with the low progesterone dosage revealed evidence of cystic glandular hyperplasia (Fig. 2c).

The results of morphometric analysis of the endometrial samples are shown in Fig. 3. The low-dosage regimen was associated with several statistically significant ($P<0{\cdot}05$) changes. In the glands there was an increase in mitotic activity and an increase in the volume fraction of gland occupied by gland cells, but a reduction in the number of supra- and subnuclear secretory vacuoles. In the stroma there was an increase in the volume fraction of the endometrium occupied by the stromal cell nuclei. On the other hand the high-dosage regimen was associated with no significant change in the glands, but a significant ($P<0{\cdot}05$) increase in the mean diameter of stromal cells.

Of particular interest are the individual results of the two women with Turner's syndrome, who were both in the high-progesterone group. They had suboptimal endometrial responses to the standard dosage regimen with histological dating of day LH+3·5 in both cases. The administration of high doses of progesterone in another cycle resulted in advancement of the endometrium in one but not in the other (histological dating of day LH+4·5 and 3·5 respectively).

Menstruation occurred 1–2 days after the cessation of oestrogen and progesterone therapy (day 29–30 of the artificial cycle) in all 14 cycles treated with the standard regimen and the seven cycles treated with the high progesterone regimens. However, in 4 of the 7 cycles (57%) treated with the low progesterone regimen, vaginal bleeding started on day 28, before the cessation of the hormone therapy.

Discussion

In this study, the effect on the endometrium around the time of implantation of three different dosages of progesterone was examined by the use of traditional dating criteria (Noyes *et al.* 1950) and by quantitative histological techniques (Li *et al.*

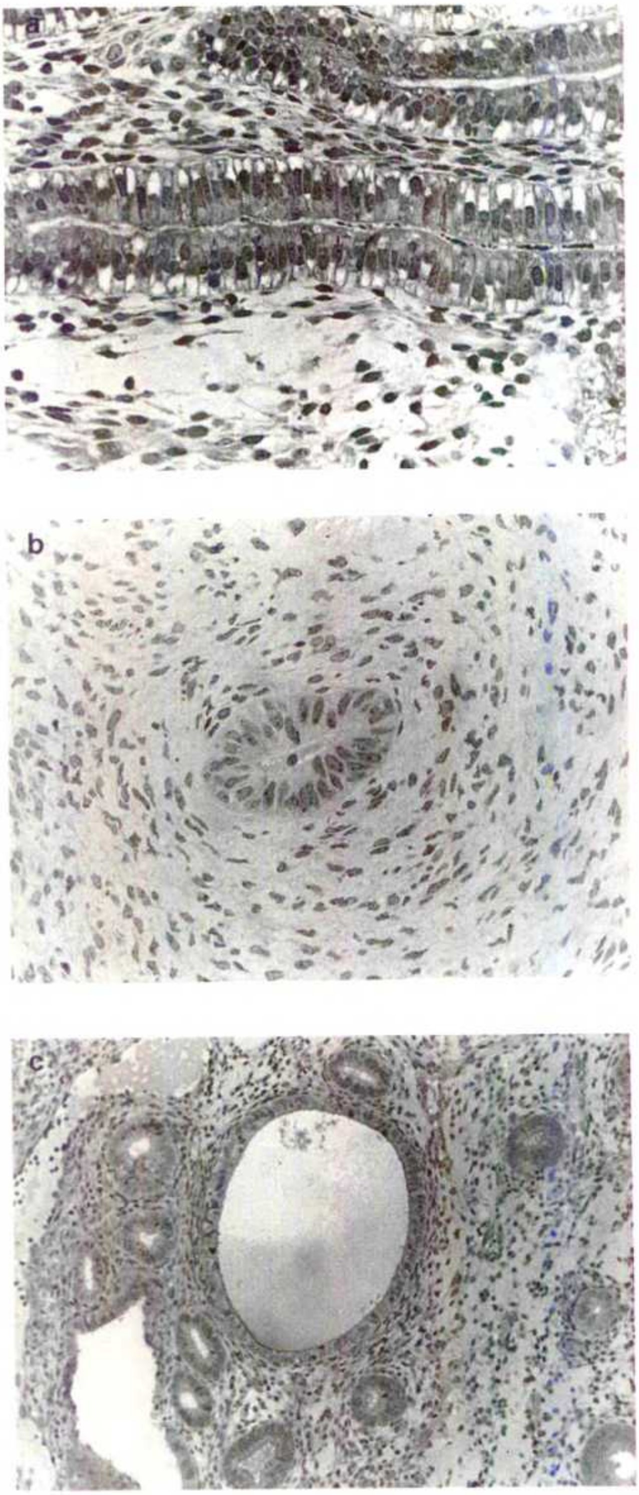

Fig. 2. The morphology of endometrial samples taken on day 19 of the artificial cycle. (a) Standard regimen (Navot *et al.* 1986), showing abundant sub-nuclear and supra-nuclear secretory vacuoles in gland cells; a small amount of secretory material is seen in the gland lumen. (b) Low progesterone regimen, showing little evidence of secretory activity in the gland cells or the gland lumen; the endometrial development in this case is clearly retarded. (c) Low progesterone regimen, showing the features of cystic glandular hyperplasia, a condition generally considered to be a consequence of unopposed oestrogenic activity.

1988; Dockery *et al.* 1990). Artificial cycles were used because this permitted the study of the endometrial response to precisely defined dosages of steroid hormones. In particular, by maintaining the same dosage of oestrogen in all cycles throughout the study, and altering only the dosage of progesterone, the effect of different progesterone levels on endometrial morphology could be examined in a controlled manner. Another strength of this study is the prospective and randomized design, so that errors due to bias and variation due to differences in individual responses were reduced. This is particularly relevant as it has been shown that there is significant inter-subject variation in the endometrial response to hormone replacement therapy in artificial cycles (Fraser *et al.* 1989; Li *et al.* 1991).

All endometrial samples in this study were taken on day 19 of the cycle, eliminating a potential source of error due to different timing. Also, efforts were made to reduce the influence of subjective interpretation by the use of established morphometric techniques, which are both objective and reproducible (Editorial 1976; Weibel 1979; Langley *et al.* 1983).

This study has recorded the various morphological changes in the glandular and stromal components of the endometrium in response to three different dosages of progesterone. Obvious differences between low and standard progesterone dosages were observed, but only a subtle difference between the standard and high progesterone dosages was found. Reducing the progesterone dosage to ⅕ that of the standard regimen resulted in significant ($P<0{\cdot}05$) increases in mitotic activity, volume fraction of gland occupied by gland cells and volume fraction of the endometrium occupied by the stromal cell nucleus, together with a significant ($P<0{\cdot}05$) reduction of the number of supra- and sub-nuclear secretory vacuoles. However, increasing the dosage of progesterone to five times that of the standard regimen did not result in any significant change in these indices. The only significant change observed at high progesterone dosage was in the stroma, where there was an increase in the mean diameter of stromal cells. These observations suggest that the glandular component of the endometrium is more sensitive to progesterone than the stroma and that it is maximally stimulated by the standard dosage of progesterone, so that any further increase has no additional effect.

Navot *et al.* (1989) attempted to address the question of whether or not secretory transformation of artificial cycles could be accelerated by high levels of progesterone. At a daily dose of 150 mg, progesterone did not advance endometrial development in the early luteal phase, but the authors claimed that endometrial maturation in the late luteal phase was accelerated. Our findings are in agreement with the former of their observations but as we did not examine endometrial morphology in the late luteal phase we are unable to comment on the latter. However, one aspect of their study open to criticism is that endometrial samples were obtained two days earlier in the cycles treated with the high dosages of progesterone than those treated with the standard dosages 'because of the anticipated hastened secretory transformation'.

The failure of high dosages of progesterone to advance endometrial development suggests that the advancement of endometrial morphology in cycles stimulated by hMG and hCG (Garcia *et al.* 1984; Sharma *et al.* 1990; Ben-Nun *et al.* 1989) may be mediated via mechanisms other than the concen-

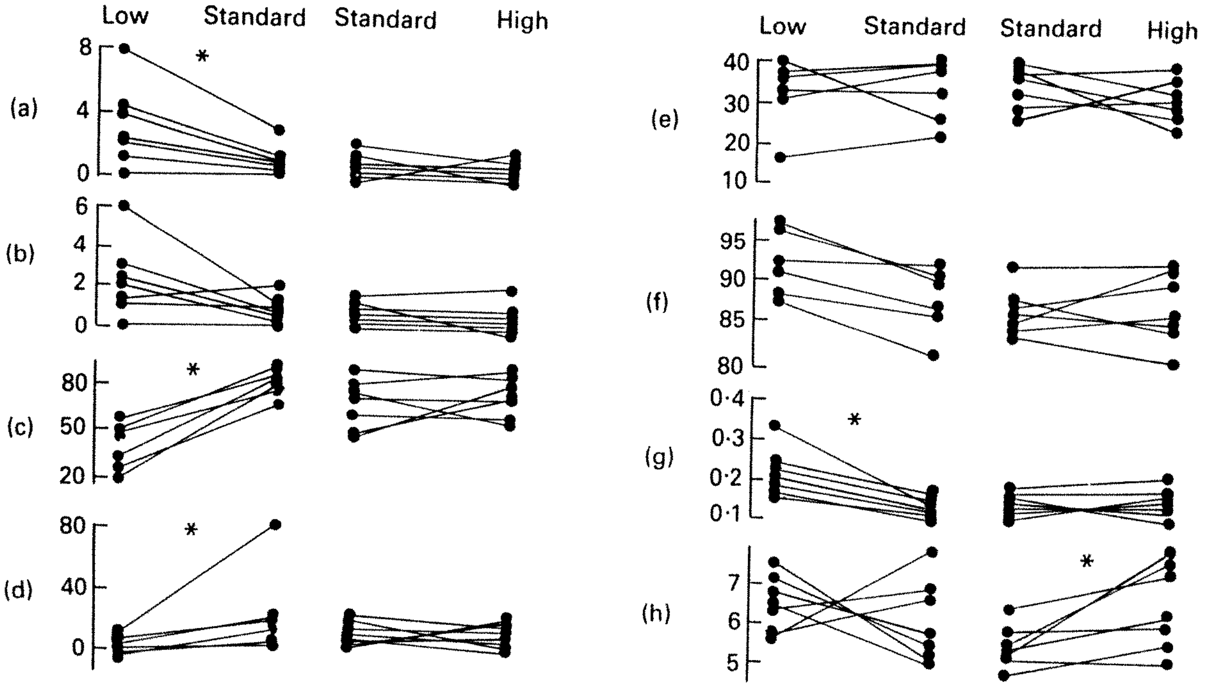

Fig. 3. Morphometric analysis of endometrial samples taken on day 19 of artificial cycles in the two treatment groups. One group received the standard and the low-dose progesterone regimens and the other received the standard and the high-dose progesterone regimens. (a) number of mitoses per 1000 glandular cells, (b) number of mitoses per 1000 stromal cells, (c) number of sub-nuclear secretory vacuoles per 100 gland cells, (d) number of supra-nuclear vacuoles per 100 gland cells, (e) volume fraction of endometrium occupied by glands (%), (f) volume fraction of gland occupied by gland cells (%), (g) volume fraction of endometrium occupied by stromal cell nucleus (%) and (h) mean stromal cell diameter (μm). * Significant difference between matched pairs ($P<0{\cdot}05$).

tration of progesterone in the luteal phase, although plasma progesterone concentration is known to be increased in hMG and hCG cycles (Cooke *et al.* 1973). Sharma *et al.* (1990) found that the progesterone concentrations on the day of follicle rupture were significantly higher in stimulated cycles (median = 16 nmol/l) than in natural cycles (median = 6·1 nmol/l); and Ben-Nun *et al.* (1990) reported that the administration of progesterone 10 h before hCG administration in stimulated cycles may advance endometrial development. Taken together, these observations suggest that a possible mechanism of advanced endometrial development in hyperstimulated cycles may be the earlier exposure of the endometrium to progesterone.

It is of interest that one of the two women with Turner's syndrome who had a suboptimal endometrial response to the standard regimen showed improvement in endometrial development in response to high dosages of progesterone whereas the other did not but it is not possible to draw conclusions from only two cases.

In the seven cycles treated with the low progesterone regimen one showed cystic glandular hyperplasia. In all of the other six there was evidence of secretory transformation in glandular cells but the number of glandular mitoses was significantly increased. The presence of secretory activity in endometrial glands cannot, alone, be taken as evidence that the dosage of progesterone was adequate. This is relevant to the assessment of the endometrium in postmenopausal women receiving hormone replacement therapy. In our opinion, both the amount of glandular secretory activity and the amount of mitotic activity should be measured to provide a complete assessment of the endometrial response.

The volume fraction of endometrium occupied by the stromal cell nuclei was significantly increased in those receiving the low progesterone regimen. The explanation for this observation could be either that the stromal cell nuclei were bigger or that the components of endometrium other than the stromal cell nuclei were smaller (for example, due to a reduction in stromal oedema) or both. We cannot deduce from our study which of these possibilities is the most likely: measurements involving absolute volumes and numbers are required to answer this question.

The mean stromal cell diameter was not different in women receiving the low and standard progesterone dosage regimens but it was significantly greater in women receiving the high progesterone dosage regimen than those receiving the standard regimen. Progesterone is known to be responsible for decidual transformation of stromal cells, which is associated with an increase in stromal cell size (Finn 1985; Dockery *et al.* 1990). However, the clinical significance of accelerated stromal cell changes induced by high progesterone dosage is uncertain and requires further investigation. A better understanding of the endometrial response to various dosages of steroid hormones is of crucial importance in the preparation of women with premature ovarian failure for treatment by donor oocyte.

Acknowledgment

We are grateful to the late Professor A. W. Rogerts DSc for his contribution to this study, which was supported by a grant from The Wellcome Trust. The secretarial support of Mrs M. Thorpe and the technical assistance of Mrs C. Piggott are appreciated.

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Received 10 January 1991
Accepted 10 September 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 325–328

CLINICAL PRACTICE

Compliance with hormone replacement therapy (HRT) after screening for post menopausal osteoporosis

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ABSTRACT

Objective To assess compliance with recommendations for hormone replacement therapy (HRT) in postmenopausal women following screening for osteoporosis.
Design A postal questionnaire sent to women an average of 8 months (range 6–12) following measurement of their bone mineral density (BMD), and recommendations regarding HRT given to the referring general practitioner.
Setting Referrals from local general practitioners. Mixed social class.
Subjects 400 postmenopausal women aged 40–69 years (average age 52).
Main outcome measures Compliance with advice and if failing to comply, reasons for not doing so.
Results Replies were received from 352 women (88%) and 74% of respondents followed advice to start, continue, or refrain from starting or continuing HRT with regard to protecting their skeleton. Those who rejected advice to take HRT mostly had concern over side effects or the efficacy or safety of treatment. Of the women who started HRT 28% subsequently stopped, the principal reasons being withdrawal bleeding and weight gain. Of the women recommended to take HRT, 39% were not taking treatment by 8 months after referral, either because they ignored advice given (22%) or because of side effects (17%).
Conclusions Screening leads to increased usage of HRT among women at most risk for osteoporosis. However, almost 40% of women with low bone mineral density were not taking HRT 8 months after referral, and therefore until improved compliance has ben demonstrated screening cannot be widely recommended.

Fractures due to osteoporosis are an enormous health problem. Fractures of the hip are the most serious, and cause 20% orthopaedic bed occupancy and a mortality of up to 20% in the first year (Cummings *et al.* 1985). The direct costs attributable to hip fracture alone in the United Kingdom in 1987 were £160 million (Royal College of Physicians 1989). Preventive treatment might be directed at falls, the usual precipitating cause of fracture, but no specific intervention has been shown to be effective (US Preventive Services Task Force report 1989). Interest has therefore centred on the preservation of premenopausal bone mass. In this regard hormone replacement therapy (HRT) is the established available treatment and has been shown to be successful in the prevention of loss of bone mass (Lindsey *et al.* 1976). In addition there is evidence that its use can reduce the prevalence of fracture (Melton *et al.* 1990).

We could attempt to treat all postmenopausal women with long term HRT but this would involve considerable cost in financial and human resources, be inappropriate for those at low risk and likely to produce poor compliance. Targetting treatment to those most at risk means identifying those patients by means of screening. Clinical risk factors have been shown to be unreliable as a means of identifying women at high risk and the only variable strongly predictive of risk of fracture is bone mineral density (Stevenson *et al.* 1989). A Royal College of Physicians Report (1989) recommended that women aged about 50 years should have their bone density measured and oestrogens offered to those below a specified cut off value.

However, the case for screening all post menopausal women by measurement of bone mineral density is still controversial, and many reviews have concluded that more research is required before it can be widely recommended (Melton *et al.* 1990). Among the unresolved issues is the expected level of compliance with recommendations for HRT. If advice on treatment following screening is not followed, then screening is of little value. The purpose of this study was to assess the response to recommendations regarding HRT given to women within 10 years of the menopause following measurement of lumbar spine and femoral neck bone mineral density.

Subject and methods

The study was performed on the first 400 postmenopausal women referred by local general practitioners from January

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1989 to an osteoporosis screening unit for measurement of their bone mineral density. Women were aged 40–69 years (average age 52) and were an average of 3 years (range 1–10) after the menopause. Bone mineral density measurement was made available to any woman whom the general practitioner wished to refer. Specific advice as a result of the scan was not given to individual women but to the referring doctor by means of 1 of 3 standard letters. The advice was either to take HRT provided there were no contraindications, wait until a further scan in 2 years time or that there was no need to take HRT to protect the skeleton. All women were screened by measurement of their lumbar spine and femoral neck bone mineral density using dual energy x-ray absorptiometry (DEXA). Measurements were made using the Hologic QDR-1000 and were compared to a normal range of values derived from 200 British women who had attended this unit previously. Women with bone mineral density below the 20th centile at the lumbar spine or femoral neck (30% of women) were recommended to take HRT, but not if there were recognised contraindications. The 50% of women with highest bone mineral density were reassured of their low risk of osteoporosis and informed that there was no necessity to take HRT. Those women with an intermediate result were offered a further scan in approximately 2 years time to assess their rate of bone loss with advice on HRT use to be delayed until then.

Each woman was contacted by letter 6–12 months (average 8 months) after the bone mineral density measurement, explaining the purpose of this study. Reasons for compliance or non-compliance with the advice given were sought. Women who stopped HRT were invited to give their reasons. Age, social class and family history of osteoporosis or fractured spine or hip had been disclosed previously by questionnaire at the time of screening, and the effect of these variables on compliance was assessed using contingency tables analysed by the $\chi 2$ test with Yates' correction using 95% confidence limits. Social class was assessed by husband's occupation, or woman's occupation if single, using the Office of Population Census and Surveys classification 1980. The family history enquiry was limited to parents, siblings and children.

Results

Of the 400 women in the study 352 (88%) returned their questionnaires. Compliance with advice offered is shown (Table 1). Of 105 women recommended to start taking HRT, 74% complied. There were 22 women already taking HRT who were advised to continue to protect their skeleton and 21 (95%) followed the advice given. Of 171 women, who were advised that there was no apparent need to take HRT to protect their skeleton, 71% did not start or continue treatment. However, after exclusion of those already taking HRT for other reasons, who could not reasonably be regarded as non compliers, the compliance rate was 85%. There were 54 women who were advised to await a further scan before deciding whether to take HRT and 74% followed this advice and did not start or continue treatment. After exclusions of those already taking HRT, the compliance rate for those advised to await a further scan rose to 83%. There was a total compliance rate with all advice offered of 74%, which rose to 82% when those already on HRT who were advised there was no need to take it or to wait 2 years were excluded.

The principal reasons for rejecting the advice to take HRT were controversy over its benefit, concern over possible side effects and concern regarding the risk of breast cancer (Table 2). Other reasons given were medical conditions such as hypertension and previous deep vein thrombosis, a desire for alternative treatment, lack of information and general practitioner being unwilling to prescribe. There were 62 women who started HRT or continued to take it though not advised, of whom 79% did so for postmenopausal symptoms without the intention for long term usage and only 19% for the prevention of osteoporosis. The reasons given for stopping HRT either before the scan or after were principally a return of regular bleeding or unwelcome weight gain (Table 2). Of those who started HRT 28% subsequently stopped, making a total of 39% of women who were recommended HRT who were not on treatment at 6 months—1 year after measurement of their bone mineral density. The results for compliance *vs* age, social class (where known) and family history are shown in Table 3. Compliance was assessed firstly in those advised to take HRT and secondly in those not currently taking HRT who were advised not to start or to wait for a further scan. Compliance was not significantly affected by age: advised to start HRT (χ^2 3·47, df 3, NS), advised not to start or wait 2 years (χ^2 1·17, df 3, NS). Compliance was also not significantly affected by social class: advised to take HRT (χ^2 2·77, df 2, NS) advised there was no necessity for HRT or wait 2 years (χ^2 6·57, df 2, NS). There was no significant effect of family history of osteoporosis or fractured hip or collapsed vertebra: advised HRT (χ^2 1·84, df 1, NS) advised no necessity for HRT or wait 2 years (χ^2 1·32, df 1, NS). Although age, family history and social class were not examined together, it was felt unlikely there would be a combined significant effect on compliance.

Table 1. Compliance with advice on the use of hormone replacement therapy (HRT) in 352 responders

Advice	No. of women	% taking HRT before scan	No. following advice (%)
Start HRT	105	(0)	78 (74)
Continue HRT	22	(100)	21 (95)
Wait 2 years & further scan	46	(0)	38 (83)
Wait 2 years & further scan	8	(100)	2 (25)
No need to start HRT	139	(0)	118 (85)
No need to continue HRT	32	(100)	3 (9)
Total	352		260 (74)

Table 2. Reasons for not starting or stopping hormone replacement therapy (HRT)

Reasons for not starting HRT		Reasons for stopping HRT	
Controversial	9	Withdrawal bleeding	8
Concern over side effects	7	Weight gain	4
Concern over breast cancer	4	Hypertension	2
High blood pressure	3	Breast tenderness	1
Deep vein thrombosis	1	Controversial	1
Other treatment sought	1	Previous deep vein thrombosis	1
Lack of information	1	High cholesterol	1
General practitioner unwilling to prescribe	1	Other side effects	4
Total	27		22

Discussion

This study has shown a high initial rate of compliance with advice offered on the need for HRT with regard to protecting the skeleton. At present less than 10% of postmenopausal women in the UK use HRT (Goddard 1990) and a recent survey by Spector *et al.* (1989) of three general practices in Greater London revealed that only 10% of all women aged 45–65 years had ever been prescribed HRT. A much higher level of HRT usage (74%) than is currently found in the general population was achieved in this study and this increased usage occurred in those women with low bone mineral density. Our rate of compliance also compares favourably with a recently published study of HRT offered to 100 women age 50–70 years with distal radial fractures (Wallace *et al.* 1990). In that study there was a 36% uptake of HRT although in the 50–55 year age range the uptake was 54%.

Table 3. Compliance with advice on use of hormone replacement therapy (HRT) by age, social class and family history of osteoporosis or fracture

Variable	Women receiving advice *n*	Followed advice *n* (%)
Advised to take HRT		
Age (years)		
<50	14	11 (79)
50–54	48	38 (79)
55–59	43	36 (84)
>60	22	14 (64)
Social class		
1 and 2	54	38 (70)
3	37	31 (84)
4 and 5	10	9 (90)
Family history		
Present	40	34 (85)
Absent	87	65 (75)
No need to start HRT*		
Age (years)		
<50	53	45 (85)
50–54	58	47 (81)
55–59	55	49 (89)
>60	17	15 (88)
Social class		
1 and 2	81	71 (88)
3	46	42 (91)
4 and 5	22	15 (68)
Family history		
Present	47	37 (79)
Absent	138	119 (86)

*Or to wait 2 years for a further scan, none of the women was taking HRT before the scan.

In the present study, however, almost 40% of women advised to start HRT were not taking treatment an average of 8 months following screening, mostly because of various side effects. It is possible that different attitudes or consultation styles of general practitioners, or a more detailed discussion of possible side effects and more information on alternative HRT preparations could have affected this outcome. However, in this present study the general practitioners involved were probably more enthusiastic than some others for HRT as they used osteoporosis screening to influence their management. The need for more education by the doctor is supported from a recent survey of women aged 50–52 years from a general practice of 12 000 women which showed that more than three quarters were interested in taking HRT for osteoporosis but over half would have liked further information and were worried about side effects (Draper & Roland 1990). There may also be a need for expert advice to be more easily available to general practitioners who will inevitably instigate most prescriptions for HRT. A recent survey showed that over half would consider prescribing HRT for the prevention of osteoporosis but there was considerable uncertainty over the balance of beneficial and harmful effects of long term usage (Wilkes & Meade 1991). Some women will not want to take HRT despite adequate education and in the future non hormonal therapy for the treatment of bone loss may be suitable for them.

There was no significant effect of age on compliance with advice to take HRT. There was also no effect of age on compliance with advice not to start HRT, for those not taking it. Also, perhaps surprisingly, there was no significant difference in the response of different social classes, and no significant effect of a positive family history of osteoporosis or fracture on compliance.

Uncertainty about the role of screening for osteoporosis will probably continue until its value in terms of the relative costs versus the benefit in terms of numbers of fractures prevented becomes clear. However, several prospective studies have now shown that the risk of osteoporotic fracture is related to bone mass (Gardsell *et al.* 1989; Wasnich *et al.* 1989; Cummings *et al.* 1990), and screening by measurement of bone mineral density offers the best means at present of detecting those most at risk who would therefore benefit most from preventive therapy. A successful screening programme requires a high level of compliance with the advice offered. These initial results from an open access screening programme demonstrate that advice is initially being followed by a high percentage of women and suggests HRT is acceptable to far more women than are treated at present. It is reasonable to assume that the women investigated are representative of those concerned about their risk of osteoporosis. However, in this group probably more motivated than the population as a whole to seek advice regarding their risk of osteoporosis, almost 40% were not taking treatment at 8 months (range 6–12) following screening. Compliance may improve with better patient education and availability of more acceptable preparations of HRT but until a high percentage of compliance with long term usage of HRT is observed, screening for osteoporosis cannot be widely recommended.

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Received 24 June 1991
Accepted 7 December 1992

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 329–332

CLINICAL PRACTICE

Benign ovarian cysts in England and Wales and in the United States

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ABSTRACT

Objective To compare the rates of hospital admission for management of ovarian cysts in England and Wales and the United States between 1972 and 1974 and 1984 and 1986; and to determine whether these rates are related to rates of early diagnosis of ovarian cancer.

Design Analysis of published and unpublished hospital discharge data based on national samples, the Hospital In-patient Enquiry (HIPE), a 10% hospital discharge sample for England and Wales, and the National Hospital Discharge Survey (NHDs), a 5% sample for the United States.

Main outcome measures Age-specific discharge rates for primary and secondary diagnoses of ovarian cyst or benign ovarian tumour.

Results There was an age-adjusted increase in discharge rates of about 8% in both countries; discharge rates in the United States were approximately double those in England and Wales in both time periods. There was no difference in the rates of early diagnosis of ovarian cancer.

Conclusions Ovarian cysts are a common cause of hospital admission in both countries. The higher rates in the United States are not associated with earlier diagnosis of ovarian cancer.

Benign ovarian cysts are a common condition that, without surgery, cannot be distinguished reliably from ovarian malignancy. Ovarian cysts can be benign neoplasms of several histological types or cysts that are hormone-dependent and usually transient. Whenever malignancy is suspected or symptoms occur, the usual recommendation for a woman with an ovarian enlargement is to admit her to hospital for excision of the cyst (Barber 1971). In women of reproductive age an ovarian malignancy is much less likely than a benign cyst or neoplasm of the ovary (Killackey 1988). Spanos (1973) suggested that a trial of pituitary suppression, such as with an oral contraceptive, might allow certain of these benign cysts to regress, and thus avoid the need for surgery in many cases. It is not known to what extent practitioners use this approach in young women although the concept is supported by evidence that users of oral contraceptives have 50–90% lower rates of hospitalization for benign ovarian cysts in both the US (Boston Collaborative Drug Surveillance Program 1974) and England (Vessey 1987). Ultrasonography is being used increasingly to diagnose and follow ovarian cysts. Most investigators believe this technique is not yet sufficiently sensitive or specific discriminating benign from malignant cysts to eliminate the need for a surgical diagnosis (Goldstein 1989; Meire 1978; Finkler 1988; Andolf 1989). The impact of sonography on the rate of hospital admission for these conditions is unknown. Currently, clinicians faced with a woman with an adnexal mass must decide when to observe and when to admit for surgery with few intermediate options and relatively little help from ancillary tests.

This paper describes the rates of hospital admission for ovarian cysts in the US and England and Wales, and considers whether these rates are related to early stage diagnosis of ovarian cancer. We contrast US rates with those in England and Wales because these countries have similar standards of gynaecological care, and similar rates of ovarian cancer (Waterhouse 1982), but very different rates of elective surgery (McPherson 1981). For both countries there exist easily retrievable data regarding hospital discharge numbers and diagnoses.

Subjects and methods

Unpublished data from the National Hospital Discharge Survey (NHDS) were obtained to estimate the number of cases of benign ovarian cysts and tumuors in the US. The NHDS is a continuous survey conducted by the National Center for Health Statistics (NCHS) that, since 1965, has collected data from the medical records of an approximately 5% national sample of patients discharged from short-stay hospitals (NCHS 1986). Among the data collected are the main diagnosis and secondary diagnoses, age, and duration of hospital stay as well as the procedures performed. For the years 1972–74 and 1984–86 we obtained estimates of the numbers of women who were discharged with a main (first-listed) or

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secondary diagnosis of ovarian cyst or benign tumour. The relative standard errors were taken from published estimates from the NCHS for each of the relevant years. We combined data from 3 years in order to decrease the effect of sampling error on the estimates. Data from years before 1972 were not sufficiently detailed with regard to the diagnoses being considered here for inclusion in this analysis. Hospital discharge rates were calculated using US Census Bureau estimates of the female population.

Hospital discharge data regarding the same conditions in England and Wales were obtained from published and unpublished tables of the Hospital In-patient Enquiry (HIPE) for the years 1972–74 and 1983–85 (Westhoff 1984; DHSS 1984, 1985, 1986). HIPE is a national survey conducted by the UK Office of Population Censuses and Surveys (OPCS) that extracts discharge data from a 10% sample of discharges from hospitals in England and Wales. HIPE served as a model for the US NHDS, and the two surveys are similar in scope and design. Denominator data regarding the female population in England and Wales were obtained from the UK Registrar Generals' Statistical Reports. All of the hospital discharge rates presented here are expressed per 100 000 women per year, and are age-adjusted to the 1984–86 US female population.

HIPE and NHDS coding of medical record data is done according to the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM). The following diagnoses were included in 1984–86: 220, benign neoplasm of the ovary; 620·0, follicular cyst; 620·1, corpus luteum cyst; and 620·2, other and unspecified cyst of the ovary. Equivalent codes from the eighth revision of the ICD were used for the 1972–74 data. The main difference is that, in ICD-8, the 'other and unspecified' ovarian cysts were included in the benign neoplasm category.

Ovarian cancer incidence, mortality and stage at diagnosis estimates for the US were obtained from published (Waterhouse 1982) and unpublished data from the cancer registries of the Surveillance, Epidemiology and End-results (SEER) program of the National Cancer Institute. For the UK, national incidence and mortality data were obtained from published tables from the OPCS (1982, 1986). Unpublished stage at diagnosis data for the UK was sought from the 15 Regional Health Authorities. East Anglia was the only region that could provide sufficiently detailed stage at diagnosis data for ovarian cancer. All cases of ovarian cancer registered in East Anglia from 1983–87 were reviewed by registry staff to tabulate the stage at diagnosis by age; there were 593 cases of epithelial ovarian cancer that were assigned a stage at registration. Both countries share the system of ovarian cancer staging developed by FIGO (1990).

Results

From 1984–86, the annual hospital discharge rate for women with a main diagnosis of an ovarian cyst was 131·3 (SE 4·1) per 100 000 women in the US. During this period, about 160 000 women were admitted to hospital each year with this main diagnosis. This represents a 34% increase over the period 1972–74 when about 120 000 women were admitted annually with a main diagnosis of ovarian cyst. The age-adjusted annual hospital discharge rate during 1972–74 was 121·1 (SE 6·7) which is about 8% less than the rate observed in 1984–86. Thus, about 27 000 of the 40 000 additional annual cases in the US during 1984–86 were due to a change in the size and the age structure of the population. Most of the remaining increase was due to an increase in the age-specific rates of admission for ovarian cysts from 194·1 to 243·4 experienced by women aged between 15 and 24 years. The effect of this increase is that American women aged 15–24 in 1984–86 had about 9000 (SE 1000) more admissions per year for these conditions than they would have had if the 1972–74 rates still applied. There was also a modest increase in the hospital discharge rates among women aged 45–64 from 61·9 to 72·6.

In England and Wales during the years 1983–85 there were about 14 000 hospital admissions for these conditions annually. The annual hospital discharge rate for women with a main diagnosis of ovarian cyst was 67·3 which is 51% of the rate in the US during the same period. The annual rate for the years 1972–74 was 61·6. Both rates are age-adjusted to the US 1984–86 population. All of the increase in the hospital discharge rate in England and Wales occurred in women aged from 25 to 44 years. In England and Wales the annual number of admissions did not increase during this period because, while the admission rates increased, the number of women in the highest risk age groups decreased. As in the US, ovarian cysts were the fourth most common reason for a gynaecological admission, and about 90% of British women discharged with this diagnosis were coded as having had an operative procedure during the admission. Although the rates are lower in England and Wales, the age distribution for each ICD category of cyst is similar to that in the US, as is the proportion of cases in each ICD category (data not shown). Women in the UK were only about one-third as likely to experience a hospital discharge with a secondary diagnosis of ovarian cyst as women in the US. In both countries the women with a secondary diagnosis of an ovarian cyst were somewhat older than those with a main diagnosis of ovarian cyst (data not shown).

Figure 1 shows the age-specific hospital discharge rates for women with a main diagnosis of ovarian cysts in the US (1984–86) and in England and Wales (1983–85). This figure includes all of the diagnostic categories together. Table 1 provides the age-specific rates in detail. In the US the cumulative incidence of admission for an ovarian cyst (main diagnosis) is about 9% by age 65; in England and Wales this is about 4%. Most of the difference between the American and English hospital discharge rates occurs among the youngest women.

During this time period in the US, estimated ovarian cancer incidence was 14·2 per 100 000 women, and annual mortality was 8·7. In the UK, incidence was 14·6, and mortality was 12·5. There were some regional differences in both countries. The analyses of stage at diagnosis, shown in Table 2 for both the US and England and Wales, include all cases of epithelial ovarian cancers diagnosed between ages 25 and 75. The results were similar when only staged cases were included. In both countries the proportion of cases diagnosed in stage 1 is small, and decreases with age. We found that a slightly greater percentage of women were diagnosed with localized disease in England and Wales compared with the US at every age, but because these percentages are based on small numbers, these differences could have easily arisen due to chance.

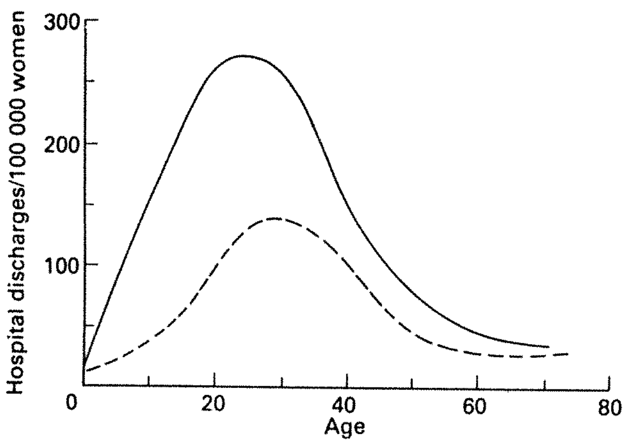

Fig. 1. Ovarian cyst hospital discharge rates in the United States and England and Wales ——, 1984–86, US; ----, 1983–85, UK.

Discussion

These data demonstrate that ovarian cysts are an extremely common cause of hospital admission with the rates in the US approximately double those experienced in England and Wales. English women who receive care for ovarian cysts in the private sector are not included in the HIPE figures; thus, the rates shown here for England and Wales are an underestimate. It is, however, unlikely that the use of private care accounts for much of the observed difference between the countries. Due to the higher rates of hysterectomy and bilateral oophorectomy in the US, the differences between the US and England and Wales would be even greater if the denominators used in calculating these rates included only those women actually at risk of an ovarian cyst (i.e. women with ovaries). Despite these limitations, both countries appeared to experience similar increases in the hospital admission rates for these conditions during the period studied, and the shape of the age-incidence curve is similar in both.

Wennberg (1989) has modelled the risk of hospital admission for a condition as a function of four determinants. These are (i) the incidence of the condition, (ii) the physician contact rate given the condition, (iii) the probability of the physician making the diagnosis, and (iv) the probability of admission given the diagnosis.

Table 1. Ovarian cyst hospital discharge rates in the United States and England and Wales (discharges 11 × 10^5 women)

Age (years)		United States 1984–86	England and Wales 1983–85
0–14		16·7	8·7
15–19		216·1	54·7
20–24		267·6	104·0
25–29		274·0	136·7
30–34		261·8	142·3
35–39		210·8	128·7
40–44		140·4	99·7
45–49		118·2	79·3
50–54		73·3	44·3
55–59		37·7	34·7
60–64		60·9	35·0
65–69		42·7	29·7
70–74			32·7
75+		36·7	29·3
Total	Crude	131·3	62·0
	Adjusted	131·3	67·3

In the reproductive age group, oral contraceptives have been identified as reducing the risk of admission for ovarian cysts. This probably occurs due to a direct reduction in the occurrence of functional (i.e., hormone dependent) cysts in women using the pill rather than due to an effect on one of the other determinants of hospital admission. Other factors that influence the incidence of functional cysts have not been described. The decrease in the use of oral contraceptives during the 1970s (Mosher 1990) as well as changes in pill formulation may have contributed to the increase in admission rates for cysts that occurred among women of reproductive age in both countries. Oral contraceptive use is somewhat more prevalent in England and Wales than in the US (Rinehart 1982, 1988), but this difference is not large enough to explain the difference in rates between the two countries. Unfortunately, neither country collected sufficiently detailed hospital discharge data during earlier years to permit assessment of admission rates for these conditions when oral contraceptives were first introduced. There is, however, some evidence that the rates in England and Wales were higher in the 1960s (Westhoff 1984).

Although the true incidence of ovarian cysts is unknown, prevalence data suggest that they are common: among 5678 asymptomatic English volunteers aged 45 years or older, an ultrasound scan revealed that 7% had an ovarian volume that was ≥mean +2SD value for morphologically normal ovaries in women of the same age, and that nearly half of these enlargements persisted on a follow-up scan (Goswamy 1986).

These large differences in admission rates in the US and Britain are at least partly due to health care system differences. The opportunity for diagnosis of an ovarian cyst exists only if a woman with a cyst visits a physician and has a pelvic examination. There are no direct measures of the number of women having a pelvic examination in either country, but the number of women having a PAP test may be a useful surrogate in the US where the performance of a PAP test is usually combined with a bimanual examination. Overall 64% of American women reported having had a PAP test within 2 years in both 1973 and 1985 (Makuc 1989). There were, not surprisingly, marked age differences with women under age 35 most likely to report having a recent PAP smear. If PAP smears are indeed indicators of pelvic examinations, the decrease in ovarian cyst hospitalizations seen starting after age 35 may be partly due to decreased opportunity for diagnosis of asymptomatic cysts. In England and Wales women most often obtain cervical smears only once every 5 years, and a bimanual examination is not as

Table 2. Stage at diagnosis of epithelial ovarian cancer in the US (SEER) and in England and Wales (East Anglia) by age

Age (years)	No. of cases at stage I/total cases (%)			
	US		England and Wales	
25–34	471/871	(54)	11/17	(65)
35–44	611/1615	(38)	15/39	(38)
45–54	1023/3574	(29)	26/95	(27)
55–64	1101/5186	(21)	32/161	(20)
64–75	732/4570	(16)	30/159	(19)

routinely included as in the US (Holland & Stewart 1990). This difference in medical practice may, in itself, result in a large difference in the number of women whose asymptomatic cysts are detected, and thus partly account for the differences between the US and British findings.

The goals of hospital admission (which usually includes a surgical procedure in both countries) are to rule out an ovarian malignancy, to relieve symptoms, or to prevent symptoms in the future. In a population-based study of English women with pathologically confirmed benign ovarian teratomas (the most common type of ovarian neoplasm), 44% were diagnosed while asymptomatic during care that was sought for unrelated reasons (Westhoff 1988). There are no other recent data that address how frequently ovarian cysts are diagnosed and removed in asymptomatic women. There are also no natural history data that describe the rate at which women with asymptomatic cysts go on to develop symptoms that require treatment.

The most important justification for the more aggressive surgical approach to ovarian enlargements in the US is the possibility of diagnosing ovarian cancer in its earliest stages. Our data, however, show no evidence of earlier ovarian cancer diagnosis in the US compared to England and Wales at any age. We should therefore all be wary of the notion that more aggressive treatment of ovarian enlargements, especially among young women, will lead to a reduction in ovarian cancer mortality.

Acknowledgments

This project was supported, in part, by the Milbank Memorial Fund. The authors gratefully acknowledge the assistance of Dr T. W. Davies and the East Anglia Tumour Registry as well as Dr A. J. Swerdlow and the Office of Population Censuses and Surveys for providing unpublished data.

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Received 17 May 1991
Accepted 20 November 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 333–337

REPRODUCTIVE SCIENCE

Spontaneous fetal reduction in multiple gestations assessed by transvaginal ultrasound

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ABSTRACT

Objective To assess the occurrence of disappearance of one or more of the fetuses in pregnancies which start as multiple gestation.
Design Observational study.
Setting Infertility section, Rambam Hospital, Haifa.
Subjects 88 women with multiple gestations, established after ovulation induction (54 twin, 26 triplet, five quadruplet, and three quintuplet) and diagnosed by transvaginal ultrasound at 5–6 weeks, in all of whom absorption of at least one gestation sac was detected at follow-up ultrasound scan.
Interventions Follow-up by serial transvaginal and later abdominal ultrasound scan throughout pregnancy.
Results Of the 54 twin gestations, 51 ended in the birth of a singleton and three in miscarriage. Of the 26 pregnancies starting as triplets, 12 ended in singleton births, 12 in twins and two miscarried. The five quadruplet gestations resulted in one singleton birth, one set of twins, two triplets, and one ended in late miscarriage. Of the three quintuplet pregnancies, two resulted in the birth of triplets, one of them after spontaneous, the other after iatrogenic fetal reduction. In the third quintuplet pregnancy, one fetus vanished spontaneously and another was subject to iatrogenic reduction, two fetuses survived and were liveborn. Of the 221 fetuses identified 107 (48%) vanished spontaneously.
Conclusion Iatrogenic fetal reduction should be delayed until 12 weeks gestation in quadruplet or higher multiple gestations, but is probably not indicated in twin and triplet gestations.

The exact rate of multiple pregnancy at implantation in the human is difficult to determine accurately because of problems of assessing the true rate of early pregnancy loss, and the frequency of twinning among pregnancies that end in miscarriage (Landy *et al.* 1982). It has been suggested that 43%–78% of conceptions are lost before 6 weeks gestation (Miller *et al.* 1980; Roberts & Lowe 1975). Landy *et al.* (1982) published an extensive review of this phenomenon, but now their conclusions need some updating and validation because they were derived from at least nine studies, using different methodologies and ultrasound systems, in different countries and continents at different times. Moreover, the widespread use of transvaginal sonography (Blumenfeld *et al.* 1988) has permitted the accurate diagnosis of multiple gestation sacs as early as the fifth week after the last menstrual period, which is considerably earlier than was possible 10 years ago.

Moreover, assisted conception using ovulatory drugs has significantly increased the occurrence of multiple gestation (Berkowitz *et al.* 1988). The increased incidence of triplet, quadruplet and higher orders of multiple gestations has resulted in the development of the technique of selective reduction, referred to by some as 'a perinatal necessity' (Berkowitz *et al.* 1988; Hobbins 1988). In order to determine the 'best' time for fetal reduction, there is a need for accurate information on spontaneous fetal reduction. We, therefore, followed 88 selected multiple gestations in which one or more fetuses disappeared spontaneously.

Subjects and methods

In a series of about 5000 pregnancies scanned by transvaginal ultrasound in the first trimester we detected 116 multiple gestations (2·3%). In 88 of these multiple pregnancies one or more of the fetuses disappeared spontaneously and these 88 pregnancies formed our study group. The women were between 25 and 40 years of age. All of them had been treated in our infertility department for ovulation induction with either clomiphene citrate (Ikaclomin, Teva, Israel) or human menopausal gonadotrophin (hMG) (Pergonal, Teva, Israel) and human chorionic gonadotrophin (hCG) (Chorigon, Teva, Israel), for either in-vivo, or in-vitro fertilization (IVF), as desribed previously by Blumenfeld & Nahhas (1988). Of the 88 pregnancies 64 were established by in-vivo fertilization and 24 by IVF/ET or GIFT. Transvaginal sonography was used to monitor follicular size during ovulation induction and, as soon as serum βhCG levels were >1000 IU/l, transvaginal sonography was used to identify the location and number of gestation sacs. The Elscint

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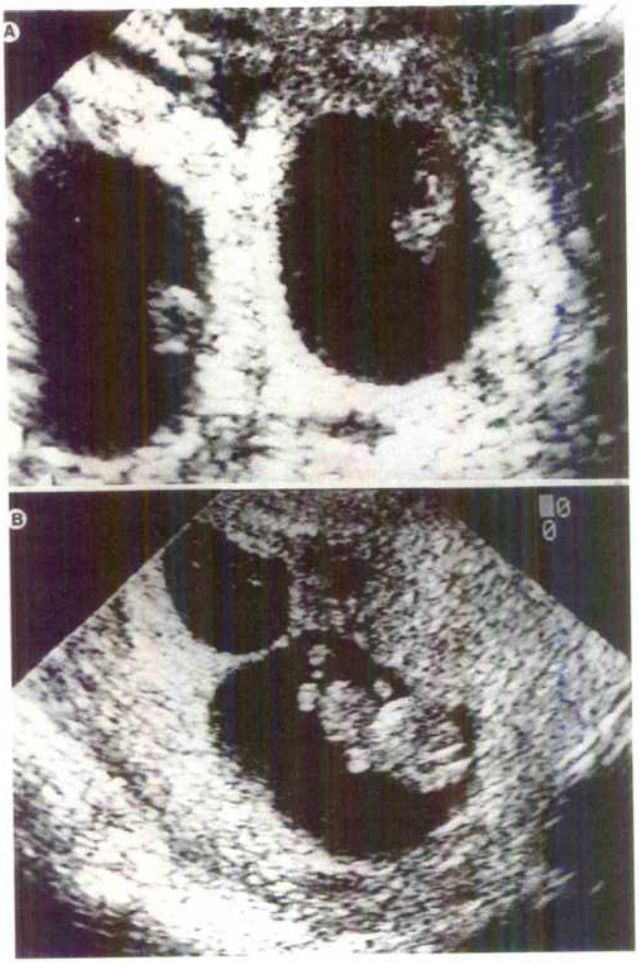

Fig. 1. Transvaginal sonography of a twin gestation (A) at 6 weeks, (B) at 11 weeks spontaneous fetal reduction to a singleton pregnancy.

ESI-1000 ultrasound imaging system (Elscint Inc., Haifa, Israel) had a 6·5 MHz vaginal probe (ESI ED-65 TV), which consisted of a mechanical sector scanner with an oscillating transducer. An intrauterine gestation sac was diagnosed by vaginal ultrasound only when the observer was positive it was not an artefact. A true intrauterine gestation sac was identified by the following characteristics: (i) a double contour, differentiating it from other intrauterine features, such as blood clot or the decidual reaction of a pseudogestational sac, at 5 weeks gestation (Timor-Tritsch *et al.* 1991); (ii) the identification of a yolk-sac within the gestation sac, from 5 weeks gestation and later; (iii) the detection of embryonic heartbeats after 6 weeks gestation.

Transvaginal sonography was repeated every 2–3 weeks until 13 weeks gestation, and afterwards abdominal sonography with a 3·5 MHz transducer (ESI ED-35) was performed every 4–8 weeks until term. Gestational age was determined by crown-rump length, biparietal diameter, head circumference, abdominal circumference, and femur length measurements, in conjunction with menstrual or ovulation dating (Blumenfeld *et al.* 1988).

Results

The initial transvaginal ultrasound examination at 5–6 weeks gestation (menstrual age) showed two gestation sacs in 54, three sacs in 26, four sacs in five and five sacs in three women (Table 1). Of the 54 pregnancies that were identified as living twin gestations (two gestation sacs and fetal heart beats detected at 6 weeks gestation) 51 resulted in the birth of a single livebirth and three ended in miscarriages (two in the first trimester and one at 16 weeks) (Table 1). Sonographic follow-up before 13 weeks failed to detect a living second twin in 50 of these 54 twin pregnancies (Fig. 1); in one pregnancy one fetus died in-utero at 25 weeks, and was removed when the second living fetus was born by caesarean section at term because of malposition. In three pregnancies, careful inspection of the placenta revealed remnants of the absorbed fetus (Fig. 2).

Of the 26 pregnancies that started with three living fetuses, one of the fetuses stopped developing in 14 pregnancies, 12 of these ended in the birth of living twins and the other two in first trimester miscarriages (Table 1). Inspection of the placenta and membranes revealed remnants of the absorbed third fetus in one pregnancy. The latest fetal death occurred at 17 weeks gestation; all other third triplets 'vanished' before 13 weeks. The

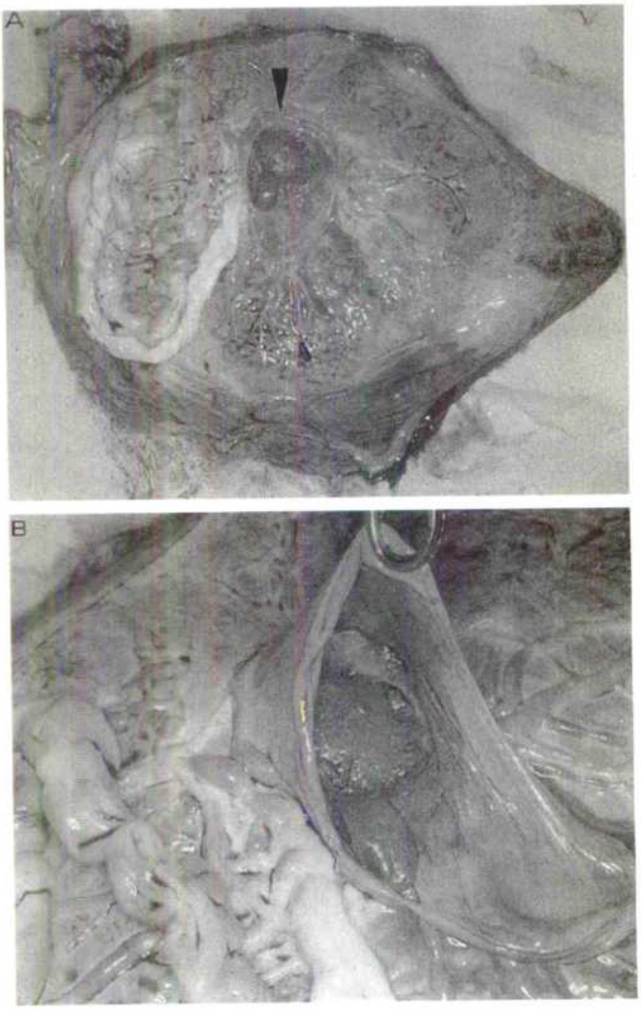

Fig. 2. The placenta and membranes of a singleton fetus in a pregnancy that started as twin gestation. Note the remnant of the second, absorbed, twin on the fetal aspect of the placenta, at lower (A) or higher (B) magnification.

Table 1. Outcome of 88 multiple gestations according to the number of gestation sacs observed during the first transvaginal ultrasound scan (TVS) and gestational ages at fetal reduction

No. of gestation sacs at first TVS	Conceptions (no. of pregnancies/ no. of fetuses)	Outcome (no. of pregnancies/no. of fetuses)				Vanished fetuses	
		Singleton	Twins	Triplets	Miscarriages	*n* (%)	Gestation (weeks)
2	54/108	51/51	—	—	3/3	54 (50)	6–25
3	26/78	12/12	12/24	—	2/4	40 (51)	6–17
4	5/20	1/1	1/2	2/6	1/3	8 (40)	6–12
5	3/15	—	1/2	2/6	—	7* (47)	6–12
Total *n* (%)							
Pregnancies	88 (100%)	64 (73%)	14 (16%)	4 (4%)	6 (7%)		
Fetuses	221 (100%)	64 (29%)	28 (13%)	12 (5%)	10 (4%)	109 (49%)	

* Two of these fetuses were subject to iatrogenic reduction.

remaining 12 pregnancies ended in the birth of one living baby at term (Table 1).

In five pregnancies, four gestation sacs containing living embryos were detected with vaginal ultrasound before 6 weeks. In two pregnancies, one fetus had 'disappeared' at the repeat scan before 10 weeks, both these pregnancies resulted in the birth of triplets by caesarean section. In the third pregnancy that started as quadruplets, one fetus vanished during the first trimester and the triplets were stillborn at 23 weeks after uterine contractions and the spontaneous rupture of membranes. Of the remaining two pregnancies one resulted in the birth of twins and the other in the birth of one baby at term.

Five sacs were detected at 6 weeks gestation in three pregnancies (Table 1). In one of these, two fetuses had 'vanished' by 11 weeks and the woman was delivered of three babies by caesarean section. In the second pregnancy, one fetus vanished by 9 weeks and the reduction of another fetus was performed by transabdominal puncture and fetal intracardiac injection of a local anaesthetic solution. This woman was delivered by caesarian section of three babies. In the third pregnancy with five gestation sacs, one fetus vanished and in four fetuses fetal heart activity was observed by vaginal ultrasound at 8 weeks gestation. One of the four fetuses was smaller than the other three. The woman gave informed consent to fetal reduction and, at 8 weeks, one sac was punctured by the transvaginal approach and the fetus was aspirated through a 16 gauge needle as described previously (Itskovitz *et al.* 1990). However, 2 days later only two fetuses were observed to be alive. This pregnancy ended in the spontaneous birth of healthy twins at 36 weeks.

As can be seen from Table 1, of the 88 multiple gestations, 64 (73%) resulted in one live birth, 14 (16%) in twins, 4 (4%) in triplets and 6 (7%) ended in miscarriage. Overall 104 babies were born alive from these 88 pregnancies. One set of twins died neonatally, in the neonatal intensive unit, one due to sepsis and the other of respiratory distress. These two babies were born at 32 weeks by caesarean section after prelabour rupture of membranes and weighed 1020 g and 1300 g. The 'take home baby rate' was 91%, of the 88 women with multiple gestations 80 were able to take home at least one baby.

Discussion

It has long been suspected that the rate of multiple pregnancy at implantation was much higher than the actual rate of multiple births. A 68% disappearance rate of multiple gestations was postulated (Landy *et al.* 1982; Levi 1976; Stoeckl 1976). The widespread use of ultrasound in the last 20 years has resulted in numerous serial ultrasound studies which have reported the 'disappearance' of at least one of two gestational rings in early pregnancy (Landy *et al.* 1982; Finberg & Birnholz 1979; Hellman *et al.* 1973; Jeanty *et al.* 1981; Kohoron & Kaufman 1974; Kurjak & Latin 1979; Levi 1976; Levi & Reimers 1978; Robinson & Caines 1977; Varma 1979).

The classic report by Levi (1976) described a cohort of 6990 women, all of whom were scanned on ten occasions. Overall 118 of them were shown to have multiple gestation sacs. Of 28 scanned before 9 weeks, follow-up data, available for 14, showed that only four sets of twins (29%) were born. Of 11 women scanned between 9 and 14 weeks, eight were followed to delivery and only three sets of twins (37%) were born. Multiple gestations diagnosed in a further 79 women scanned after 15 weeks resulted in 77 sets of twins, one set of triplets and one singleton birth (a fetus papyraceous had been diagnosed by scan at 16 weeks in this pregnancy). Thus Levi (1976) noted a 71% 'disappearance' rate of twin gestation when the diagnosis was made before 10 weeks. These data were based on abdominal ultrasound studies and we were interested to compare them with our findings obtained with transvaginal ultrasound which is able to diagnose multiple gestations accurately between 4 and 8 weeks gestation.

Of the 88 pregnancies identified in our study as multiple gestations by transvaginal ultrasound before 6 weeks gestation, 64 (73%) resulted in living singleton babies and 14 (20%) in multiple births (Table 1). The number of babies born in each multiple pregnancy was smaller than the number of gestation sacs seen at 5–6 weeks gestation. The other 18 twin gestations identified at 6 weeks gestation in our infertile population continued without fetal loss to delivery. Thus spontaneous fetal reduction occurred in 88 of 106 multiple pregnancies, a rate of 83%. Table 1 shows that 50% (111 of 121) of the multiple fetuses detected at 6 weeks vanished. Our disappearance rate of 50% of fetuses in 83% of multiple gestations after 6 weeks is comparable with rates of 71%–78% reported by Levi (1976) and Levi & Reimers (1978) by 10 weeks since the loss rate in both singleton or multiple gestations would be expected to decrease as pregnancy advances (Landy *et al.* 1982).

Levi & Reimers (1978) described 159 women with multiple gestation sacs among 3161 (5%) scanned by ultrasound during the first trimester. All 89 women found to have multiple gestations after 14 weeks gave birth to more than one baby, but in 78% of the twin gestations diagnosed by 10 weeks a fetus vanished. We found a similar disappearance rate, however, in contrast to Levi & Reimers (1978) in our series fetal loss occurred also after 14 weeks gestation, one of the twin fetuses died at 25 weeks and one of the triplet fetuses at 17 weeks. None of the fetuses in the quadruplet and quintuplet pregnancies was lost after 12 weeks. These data are of relevance when considering the advisability of iatrogenic fetal reduction in multiple gestations (Berkowitz *et al.* 1988; Hobbins 1988; Itakovitz *et al.* 1990). This innovative procedure may offer an important option to women with a desperately wanted pregnancy, but with a dangerously large number of fetuses. Those who view abortion under any circumstances as immoral will find selective reduction ethically unacceptable. Those who think that abortion may be appropriate under special circumstances must wrestle with the concept of sacrificing some fetuses so that others can survive (Hobbins 1988).

The two important questions are whether to offer this procedure to any woman with a multiple pregnancy and, if so, when is the 'best' time to perform selective fetal reduction? The perinatal oucome for twins in the western world is good enough to indicate that at least two fetuses should be spared when selective reduction is performed, and that the procedure should not be offered to women with a normal twin pregnancy (Berkowitz *et al.* 1988). However, women carrying four or more fetuses are at substantial risk of adverse outcomes, and could be offered selective fetal reduction (Berkowitz *et al.* 1988).

Triplet gestations present a considerable dilemma for both the women and their physicians. Berkowitz *et al.* (1988) advocate strongly that before fetal reduction a woman must be counselled extensively about its potential risks and that the procedure should not be undertaken unless the couple is prepared to lose the entire pregnancy as a consequence. Indeed, in the series reported by Berkowitz *et al.* (1988) four of the 12 pregnancies were lost. Our experience of triplet pregnancies shows that of 26 triplet gestations 46% underwent spontaneous reduction to twin gestation before 12 weeks, the latest fetal loss occurred at 17 weeks. The two women with quintuplet pregnancies in our series who accepted iatrogenic reduction to three fetuses, had only four living fetuses at the time of the procedure. In one of these pregnancies one of the remaining three living fetuses died in-utero within 48 h of the procedure. The other quintuplet gestation had become a triplet gestation spontaneously by 12 weeks and resulted in three liveborn babies. We tend to agree with Berkowitz *et al.* (1988) that reduction should be offered at 12 weeks when there are living quadruplet and quintuplet fetuses, but that this might be unwise with triplets because of the chance of spontaneous reduction even at 17 weeks.

About 5000 first trimester transvaginal ultrasound scans in our department detected 116 multiple gestations (2·3%). This rate is similar to the rates of 1·9% reported by Levi & Reimers (1978) and of 2% reported by Varma (1979) but smaller than the calculated rate of multiple pregnancy of 7·6 ± 3·9% as suggested by Jeanty *et al.* (1980, 1981). All these rates are significantly higher than the generally accepted twinning rate of one in eighty (Jeanty *et al.* 1981).

In three of our pregnancies examination of the placenta and membranes showed remnants of the absorbed fetus (Fig. 2). This is similar to the experience of Timor-Tritsch *et al.* (1991). In their attempts to explain the high twin disappearance rate, Landy *et al.* (1982) mention one of the most obvious sources of false-positive errors, such as the low-quality images produced by the ultrasound equipment at that time. Although the transvaginal sonographic equipment used in our study has an excellent resolution, the rates remain similar to those published previously by Landy *et al.* (1982); Levi (1976) and Levi & Reimers (1978).

We conclude that even with accurate assessment by the high resolution transvaginal ultrasound, the frequency of human multiple conception is considerably higher than has been believed previously. Familiarity with accurate rates of spontaneous fetal reduction has an important influence on the need for and timing of iatrogenic fetal reduction.

Acknowledgment

The invaluable assistance of Bathia Navar in typing this manuscript is thankfully acknowledged.

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Received 1 July 1991
Accepted 26 November 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 338–341

REPRODUCTIVE SCIENCE

Plasma concentrations of motilin and somatostatin are increased in late pregnancy and postpartum

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ABSTRACT

Objective To examine plasma levels of motilin and somatostatin throughout pregnancy.

Design Prospective observational study.

Setting University Hospital, Norway.

Subjects Eight healthy pregnant women (aged 24–38 years) six of them primigravidae and eight healthy non-pregnant women of similar age with ovulatory menstrual cycles.

Interventions In the pregnant women blood samples were obtained at 4-week intervals from 8 weeks gestation throughout pregnancy and again at 5 days and 28 days postpartum. In the non-pregnant controls blood samples were obtained on cycle days 4, 7, 10, 13, 14, 15, 18, 21 and 24.

Main outcome measures Plasma levels of motilin and somatostatin.

Results Plasma concentrations of both motilin and somatostatin rose continuously during pregnancy, and motilin levels increased still further to a peak of 165·1 (SE 35·8) pmol/l at 5 days postpartum. Plasma motilin levels were significantly higher during the third trimester and at 5 days postpartum compared with non-pregnant controls ($P<0{\cdot}0001$). The highest plasma somatostatin levels were found at 40 weeks gestation and at 5 days postpartum (mean 32·1 SE 1·1 pmol/l). Somatostatin levels were significantly higher during the second and third trimester and the postpartum period compared with levels in the follicular phase of the non-pregnant controls ($P<0{\cdot}0001$).

Conclusions Circulating levels of motilin cannot play a major role in the relaxation of the gut in pregnancy, but somatostatin may play a part in regulating motility.

Pregnancy is associated with a generalized relaxation of the gastrointestinal tract (Hytten 1980), mainly thought to be effected by the smooth-muscle relaxing properties of progesterone (Bruce *et al.* 1979; Schaffer *et al.* 1984), but it has also been suggested that gastrointestinal hypomotility may partly be due to decreased circulating motilin levels (Christofides *et al.* 1982). Motilin, a basic polypeptide of 22 amino acids, was originally demonstrated after the observation that alkalinization of the duodenum in dogs increased the motor activity in denervated gastric pouches (Brown *et al.* 1966). Later studies have confirmed that motilin is also of importance for the initiation of the antro-duodenal migrating complexes in man (Vantrappen *et al.* 1979; Janssens *et al.* 1983). We have shown previously that plasma motilin concentrations during late pregnancy remained unchanged compared with the levels obtained one year postpartum, and that plasma motilin levels were even elevated shortly after parturition (Jenssen *et al.* 1986a). We therefore suggested that it seemed unlikely that motilin was of any importance to the gastrointestinal hypomotility seen in pregnancy. The present longitudinal study was aimed to characterize more closely the patterns of change in plasma motilin concentrations during pregnancy and the postpartum period compared with non-pregnant controls and to examine whether altered circulating motilin levels could play a role for the relaxation of the gastrointestinal tract in pregnancy.

Somatostatin, another gastrointestinal peptide exerting effects on the smooth-muscle cells of the gastrointestinal tract, was also measured. Somatostatin is a physiological inhibitor of motilin release (Jenssen *et al.* 1986b) and has been shown to inhibit both gastric emptying and gallbladder contractions (McIntosh 1985), but stimulates jejunal contractions (Peeters *et al.* 1983).

Subjects and methods

Eight healthy pregnant women (aged 24 to 38 years, mean 31·0 years), six of them primigravidae, participated in the study. All women completed an uncomplicated pregnancy with delivery of full-term and healthy singleton babies of appropriate weight. The postpartum period was uneventful in all women.

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Gestational age was determined accurately by ultrasound examination in early pregnancy. None of these women had taken any drugs, apart from iron supplements, for at least three months before conception. All women were of normal weight before conception, and their weight gain during pregnancy was within a normal range. None of the women suffered from serious gastrointestinal complaints such as nausea, heartburn, or constipation during the study period.

Eight healthy women (aged 21 to 37 years, mean 26·1 years) of normal weight served as non-pregnant controls, and were studied during one spontaneous menstrual cycle; the actual cycle length varied between 27 and 32 days (mean 29·4 days). All women had ovulatory menstrual cycles, confirmed by serum progesterone levels exceeding 25 nmol/l in the luteal phase. Data from this group have been published before (Holst *et al.* 1989).

All women who participated in the study gave their informed consent. None of the subjects had gastrointestinal diseases or any other chronic illness.

Blood sampling was performed between 0800 and 1000 hours after an overnight fast as described previously (Holst *et al.* 1986). On each occasion two blood samples were obtained at 10 min intervals using an indwelling antecubital venous catheter. The plasma concentration of each substance was determined as the mean of the values measured in these two samples. In the pregnant women, blood samples were obtained every 4 weeks after 7 weeks gestation, in weeks 8, 12, 16, 20, 24, 28, 32, 36 and 40. Blood samples were also obtained 5 days and 4 weeks after delivery.

In the non-pregnant control group, blood samples were obtained on cycle days 4, 7, 10, 13, 14, 15, 18, 21 and 24 after the onset of the last menstrual period. Samples were allocated to the follicular phase, midcycle, and luteal phase, respectively, as described previously (Holst *et al.* 1989). Briefly, midcycle was defined as the day with maximum serum luteinizing hormone (LH) levels ± 1 day. The follicular phase was defined as the period 4 days or more before the day with maximum LH levels. The luteal phase was defined as cycle days with serum progesterone levels above 25 nmol/l.

The plasma concentrations of motilin and somatostatin were measured by radioimmunoassay as described previously (Jenssen *et al.* 1984; Burhol *et al.* 1984). The intra-assay and inter-assay variations were < 10% for both assays.

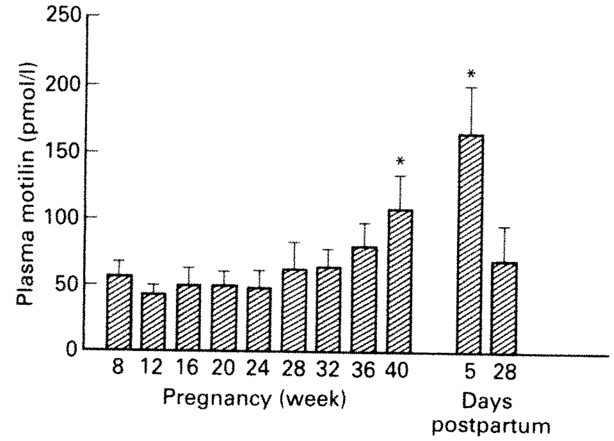

Fig. 1. Plasma concentrations of motilin in eight women during pregnancy (weeks 8 to 40) and postpartum (5 days and 4 weeks). Mean ± SEM. The asterisks indicate significant difference from the concentration at week 8 ($P<0{\cdot}0001$, two-way AOV).

Statistical analyses

The data were normally distributed, and we therefore applied analysis of variance (AOV) for statistical purposes. Two-way AOV was used for comparisons within groups, and one-way AOV for comparisons between groups. Thus, two-way AOV and pairwise comparison based on least significant difference were used to evaluate differences between mean hormone levels at the different periods of gestation (i.e., weeks 8–40) as well as postpartum. One-way AOV and pairwise comparison based on least significant difference were used to estimate differences between mean hormone levels in the first (weeks 8–12), second (weeks 16–28), and third trimester (weeks 32–40) of pregnancy; during the postpartum period (5 days and 4 weeks after delivery); as well as in non-pregnant controls (i.e. in the follicular phase, midcycle, and luteal phase of spontaneous menstrual cycles). *P*-values <0·05 were considered significant. The results are expressed as the mean (SEM) values.

Results

Motilin

Compared with week 8 (mean 56·1 SEM 11·5 pmol/l), plasma motilin levels increased non-significantly to 79·1 (SEM 18·4) pmol/l in week 36 (Fig. 1). At term the motilin concentration (mean 107·9 SEM 25·8 pmol/l) was significantly increased compared with levels in week 8 ($P<0{\cdot}0001$ by two-way AOV). A further increase in plasma motilin levels was observed by day 5 after delivery (mean 165·1 SEM 35·8 pmol/l, $P<0{\cdot}0001$). At 4 weeks postpartum plasma motilin concentrations were similar to the levels found between 8 and 40 weeks gestation (Fig. 1).

Plasma motilin levels in the last trimester of pregnancy were significantly increased compared with non-pregnant controls ($P<0{\cdot}0001$ by one-way AOV, Table 1).

Table 1. Plasma concentrations of motilin and somatostatin in eight pregnant women during the first (weeks 8–12), second (weeks 16–28) and third trimester of pregnancy (weeks 32–40), and at 5 days and 4 weeks postpartum and in eight non-pregnant controls during one spontaneous menstrual cycle

Reproductive phase	Motilin (pmol/l)		Somatostatin (pmol/l)	
	Mean	(SEM)	Mean	(SEM)
Trimester of pregnancy				
First	49·1	(6·8)	26·3	(0·5)^{c}
Second	51·7	(7·5)	29·3	(0·4)^{a,b}
Third	83·6	(11·6)^{a,b,c}	30·5	(0·7)^{a,b}
Postpartum (days)				
5	165·1	(35·8)^{a,b,c}	32·1	(1·3)^{a,b}
28	68·6	(27·1)	30·1	(0·9)^{a,b}
Non-pregnant menstrual cycle				
Follicular phase	16·0	(0·7)	23·9	(0·4)
Midcycle	13·0	(1·1)	24·9	(1·1)
Luteal phase	19·7	(1·5)	29·5	(1·4)

‡$P<0{\cdot}0001$ by one-way AOV: ^{a}*vs* follicular phase, ^{b}*vs* midcycle, ^{c}*vs* luteal phase.

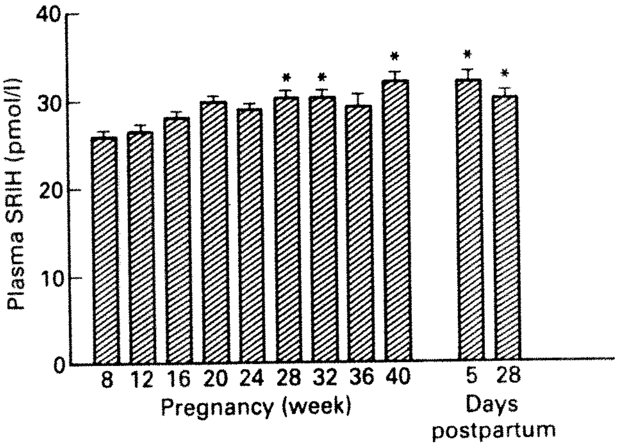

Fig. 2. Plasma concentrations of somatostatin (SRIH) in eight women during pregnancy (weeks 8 to 40) and postpartum (5 days and 4 weeks). Mean ± SEM. The asterisks indicate significant differences from the concentration at week 8 ($P<0{\cdot}0001$, two-way AOV).

Plasma motilin concentrations five days postpartum were significantly higher than the levels obtained during the first and second trimester of pregnancy as well as in the non-pregnant controls ($P<0{\cdot}0001$ by one-way AOV, Table 1). On the other hand, plasma motilin levels measured 4 weeks after delivery were not different from those obtained during pregnancy, or in control women (Table 1).

Somatostatin

Plasma somatostatin levels increased from week 8 (mean 26·0 SEM 0·8 pmol/l) until term (mean 32·1 SEM 1·1 pmol/l, Fig. 2). Somatostatin concentrations were significantly elevated in the gestational weeks 28, 32, and 40 compared with concentrations in week 8 ($P<0{\cdot}0001$ by two-way AOV). Moreover, plasma somatostatin levels both by day 5 and 4 weeks after delivery were significantly increased compared with concentrations at week 8 ($P<0{\cdot}0001$).

Plasma somatostatin concentrations during the second and third trimester were similar to the values seen during the luteal phase of the menstrual cycle, but significantly higher than concentrations during the follicular phase and at midcycle ($P<0{\cdot}0001$ by one-way AOV, Table 1). Somatostatin concentrations during the first trimester, however, did not differ from the levels found during the follicular phase and at midcycle, and were significantly lower than levels measured in the luteal phase of the spontaneous menstrual cycle ($P<0{\cdot}0001$, Table 1).

Plasma somatostatin concentrations 5 days and 4 weeks postpartum were significantly higher than levels obtained both during the first trimester of pregnancy and during the follicular phase and at midcycle of the menstrual cycle ($P<0{\cdot}0001$ by one-way AOV, Table 1).

Discussion

The present longitudinal study shows that plasma levels of motilin as well as of somatostatin are significantly increased in the third trimester of pregnancy and postpartum compared with non-pregnant controls.

In contrast to the present findings, Christofides *et al.* (1982) have reported decreased plasm motilin concentrations in gestational weeks 16 and 36 and these increased to normal non-pregnant levels within one week after delivery. The reason for these apparently conflicting results remains unclear, but differences in RIA methodology and study design, such as sampling frequency, may be a possible explanation.

It is thought that motilin release is mainly mediated by ingestion of meals and vagal tone (Jenssen *et al.* 1984). During late pregnancy and postpartum, however, additional, and as yet unknown factors must be operative to cause the increased plasma motilin levels.

Circulating somatostatin levels during pregnancy have to our knowledge been the subject of only one previous investigation. In that cross-sectional study, no changes in plasma somatostatin levels were found in the second and third trimester of pregnancy when compared with non-pregnant controls (Webb *et al.*, 1985). The difference in study design compared to our longitudinal investigation may be responsible for the contradictory results obtained.

The possible reasons for the increased somatostatin release during late pregnancy and postpartum are unknown. In the non-pregnant state the splanchnic area is the main source of circulating somatostatin (McIntosh 1985); in pregnancy, however, the placenta apparently contributes to the increased secretion (Lee *et al.* 1982). Moreover, somatostatin secretion is regulated by ingested and circulating nutrients, and is influenced by a number of other factors, including vagal tone, cholinergic and adrenergic mechanisms, histamine, prostaglandins, opiates, and a variety of gastrointestinal regulatory peptides (McIntosh 1985), all of which may lead to increasing somatostatin levels in late pregnancy and the postpartum period.

Motilin is of importance for the initiation of the antroduodenal migrating complexes (Vantrappen *et al.* 1979; Janssens *et al.* 1983). Therefore, our finding of increased plasma motilin levels does not support the concept of motilin playing a role in the gastrointestinal hypomotility of pregnancy. Rather, it may be speculated whether the elevated plasma motilin concentrations in late pregnancy and postpartum may represent a compensatory mechanism to restore gastrointestinal motility. Our observation of increased plasma somatostatin concentrations during late pregnancy and also postpartum could be related to gastrointestinal function, since somatostatin has been shown to inhibit both gastric emptying and gall-bladder contractions (McIntosh 1985), whereas it stimulates jejunal contractions (Peeters *et al.* 1983). Future studies examining the effects of gastrointestinal regulatory peptides and sex hormones on gastrointestinal motility during pregnancy *in vitro* or *in vivo* are obviously needed.

From our findings we may conclude that altered circulating motilin levels cannot play a major role for the relaxation of the gastrointestinal tract that occurs in pregnancy. Therefore, available evidence suggests that increased circulating progesterone levels may be the main factor causing the gastrointestinal hypomotility, although other gastrointestinal regulatory peptides (such as somatostatin) may also be of importance in regulating the motility of the gastrointestinal tract in pregnant women.

Acknowledgments

We appreciate the superb technical assistance of Aase Lund

Bendikssen, Jorun Eikrem, and Elin Øien Johnsen. This work was supported by grants from Helga Sembs Fond, Norsk Råd til Bekjempelse av Fordøyelsessykdommer, Nordisk Insulinfond, Den norske Kreftforening, The Norwegian Research Council for Science and the Humanities, and Aakres Fond.

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Received 26 April 1991
Accepted 3 December1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 342–343

REPRODUCTIVE SCIENCE

Passive maternal smoking and birthweight in a South Indian population

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ABSTRACT

Objective To determine the effects of passive maternal smoking on birthweight.
Design Cohort of consecutive singleton live births.
Setting Teaching hospital in South India.
Subjects 994 infants and their mothers.
Main outcome measure Birthweight.
Results All the women were themselves non-smokers; 520 (52%) were passive smokers while the remainder were not exposed to tobacco smoke. Infants born to passive smokers were on the average 55 g lighter than those born to non-smokers. Passive smoking was associated with a decrease in birthweight of 63 g (95% CI 12–114 g) even after adjusting for other variables known to affect birthweight.

Attention has lately been focused on the effects on health of passively inhaled smoke. Passive smoking or side stream smoking or second hand smoking appears to be hazardous in its own right (Jarvis *et al.* 1983). Studies have found a direct relation between passive smoking and childhood respiratory illness (Pedreira *et al.* 1985). Reports on passive smoking in pregnancy (Martin & Bracken, 1986; Rubin *et al.* 1986; Mathai *et al.* 1990) suggest that passive maternal smoking reduces birthweight, but those studies have been in populations were smoking among women is common. It may be possible that some women in those studies could have been wrongly classified as passive smokers when they were in fact active smokers. Smoking among women in Vellore is almost non-existent. The objective of this study was to investigate the effects of passive maternal smoking on birthweight in a group of non-smokers from an ethnic group hitherto not studied.

Subjects and methods

The study group was a cohort of 994 singleton live births occurring in women who had received antenatal and intrapartum care in the Department of Obstetrics & Gynaecology of the Christian Medical College Hospital, Vellore, between January and May 1990. Mothers were interviewed by one of two investigators using a questionnaire. Each mother was asked if she smoked or used tobacco in any other form, and if there was anyone in the household who smoked tobacco. Obstetric and medical details of each mother were recorded from case notes as was birthweight which was recorded in the delivery suite within 30 min of birth. The best estimate of gestation obtained from menstrual history, sonographic examination and by examination of the newborn was recorded.

Data analyses were done using the SPSS PC package. Statistical methods used were analysis of variance, χ^2-test and stepwise multiple regression analysis.

Results

None of the 994 women used tobacco in any form but 520 (52%) lived with smokers and were therefore considered to be passive smokers.

Demographic characteristics of the two groups are presented in Table 1. Whereas the two groups were comparable, for maternal age and height, there were statistically significant differences between the groups for parity, social class and maternal diet. There were more passive smokers with parity greater than three and from lower social classes while there were more vegetarians among the non-smokers. However, consumption of meat by non vegetarians occurred once a week or less frequently in 89·5% of non-smokers and in 95% of passive smokers.

The mean birthweight of infants born to passive smokers was 2890 (SD 414) g and was on the average 55 g lighter than the mean birthweight of infants born to non-smokers, 2945 (SD 447) g. Thirteen (2·5%) infants born to passive smokers and 12 (2·5%) infants born to non-smokers weighed 2000 g or less at birth.

The median gestation at birth was 39 weeks in both groups and the 5th and 95th centiles were 36 and 41 weeks in the passive smokers group and 37 and 41 weeks in the non-smokers

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Table 1. Demographic characteristics

Variable	Non-smokers (n = 474)	Passive smokers (n = 520)	Significance	
Maternal age (years)	24·9 (4·1)	24·4 (3·9)	F = 2·98	NS
Maternal height (cm)	151·6 (6·1)	151·2 (6·0)	F = 0·85	NS
Vegetarian	160 (33·8%)	61 (11·7%)	χ^2 = 68·94	P<0·0001
Parity				
1	184 (38·8%)	153 (29·4%)	χ^2 = 14·63	P = 0·007
2–3	254 (53·6%)	298 (57·3%)		
4+	36 (7·6%)	69 (13·3%)		
Social class*				
1 & 2	26 (5·5%)	8 (1·5%)	χ^2 = 54·0	P<0·0001
3N & 3M	257 (54·7%)	189 (36·4%)		
4 & 5	187 (39·8%)	323 (62·1%)		
Not recorded	4			

* Corresponding to those used by the UK Registrar General.
Results are mean (SD) or n (%) values as appropriate.

group. There were 30 (5·8%) preterm births among the passive smokers and 18 (3·8%) among the non-smokers; this difference was not statistically significant. Further, there were no statistically significant differences between the two groups as regards infant sex, intrapartum problems, method of delivery, Apgar scores or early neonatal morbidity.

Birthweight was regressed against maternal age, height, diet, parity, social class, gestation at birth and its square, sex of the infant and passive smoking (Table 2). Passive smoking was significantly associated (P = 0·015) with a decrease of 63 g (95% CI 12–114 g) in birthweight after adjusting for other factors known to affect birthweight. This regression model explained 15·5% of the variation in birthweight.

Discussion

This is the first report on the effects of passive maternal smoking on birthweight from a population in which women smokers are uncommon. Passive maternal smoking was associated with a decrease of 63 g in birthweight after adjusting for other variables affecting birthweight, but since most women in this study were unable to quantify their exposure to tobacco smoke, a dose-response relation between passive smoking and birthweight could not be calculated.

Mathai *et al.* (1980) reported a decrease in birthweight of 66 g associated with passive smoking but as there were only 56 passive smokers in that study, this difference was not statistically significant. Earlier, Martin & Bracken (1986) reported a 24 g decrease in birthweight associated with passive smoking and Rubin *et al.* (1986) reported a decrease of 6 g for every cigarette passively smoked in a day. These differences in birthweight are statistically significant, but what is the clinical relevance to these findings?

Table 2. Factors affecting birthweight

Variable	Coefficient	SE	Significance
Gestation	630·017	235·444	0·008
Maternal height	11·984	2·106	<0·0001
Sex	−115·119	25·508	<0·0001
Maternal age	7·105	3·460	0·04
(Gestation)^2	−7·153	3·064	0·02
Parity	42·678	16·289	0·009
Passive smoking	−62·821	25·862	0·015
(Constant)	−12514·461	4522·183	0·006

The outcome measured in all studies on passive maternal smoking has been birthweight. While birthweight is an easily measurable outcome, it is possible that there could be minor developmental delays and other long term morbidity in these babies born to passive smokers which have not been measured. Some of these may appear quite late in childhood. For example Butler a Goldstein (1973) reported that at the age of 11 years, children born to smokers were 1·5 cm shorter, and had a 9 month handicap in reading and mathematics when compared to those who had been born to non-smokers. These differences persisted even after allowing for social factors in the home environment and biological factors that could affect growth and development.

The answer therefore is not yet clear. But until such time as it can be proved that passive smoking in pregnancy causes no harm, it may be worthwhile to caution parents about possible hazards of exposure to tobacco smoke in pregnancy.

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Received 3 July 1991
Accepted 5 November 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 344–348

CASE REPORTS

Severe endometriosis treated with gonadotrophin releasing hormone agonist and continuous combined hormone replacement therapy

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Case report

A healthy, single woman presented in 1988 at the age of 32 with constipation, deep dyspareunia and severe dysmenorrhoea. The symptoms were interfering with her life as a singer to the extent that she was considering stopping work.

Bimanual examination revealed a rectovaginal mass, extending into the pouch of Douglas and involving both uterosacral ligaments. A mid-rectal constriction was palpated on digital examination with ballooning of the empty rectum distal to this. A subsequent examination under anaesthesia confirmed these findings. A computed tomogram of the pelvis displayed an encircling soft tissue mass around the rectum with extension into the pouch of Douglas. Barium contrast studies of the large bowel demonstrated smooth indentation and constriction of the mid-rectum. Cystoscopy, endometrial curettings and cervical biopsy plus cytology were normal.

Laparoscopy, done in consultation with a rectal surgeon, revealed extensive inflammation of the pelvic organs. The uterus was tilted towards the left and was bound by dense adhesions to the rectum. Multiple endometriotic deposits were seen. In the absence of other pathology, laparotomy was not carried out.

The diagnosis of endometriosis was explained and the patient was treated with medroxyprogesterone acetate (Provera, Upjohn), 50 mg daily, she soon became amenorrhoeic. Despite this regimen, dyspareunia and constipation persisted and the side-effects of high dose progestogens were poorly tolerated by the patient: she complained particularly of weight gain, loss of libido and 'depression'. At this stage she was most unhappy, often unable to work and finding it impossible to have intercourse.

Four months later, she was treated with danazol (Danol, Sanofi Winthrop), 200 mg three times daily, but after 6 months she decided to stop treatment because of unpleasant side effects. Two months later she was admitted as an emergency under the urologists with severe left loin pain. Ultrasound examination and intravenous urography confirmed a left hydronephrosis and hydroureter with obstruction at the lower third of the ureter. The obstruction was initially decompressed by percutaneous nephrostomy drainage and at subsequent laparotomy, dense endometriotic adhesions were found to be constricting the distal left ureter. The ureter was divided and re-implanted into the bladder via Psoas hitch procedure.

The patient at all times insisted that she did not want to have pelvic surgery because she wished to retain her fertility. Accordingly, 2 months later she was treated with goserelin (Zoladex, ICI), 3·6 mg, given by deep subcutaneous implant (every 28 days) supplemented by 0·625 mg of conjugated oestrogens (Premarin, Wyeth) and 5 mg medroxyprogesterone acetate (Provera, Upjohn) daily. Before starting treatment, bone mineral density (BMD) was measured by dual energy x-ray absorptiometry (DEXA). The lumbar spine (L2–L4) and femoral neck BMD was normal.

Three months later the patient reported a considerable improvement in her symptoms. She was amenorrhoeic, intercourse was painfree, bowel function was normal and body weight had returned to normal. The 'depression' she earlier described had resolved. Examination revealed minimal pelvic tenderness, the rectovaginal mass was softer in consistency with less rectal constriction.

The patient has now taken this treatment for 12 months and reports feeling extremely well. She is again able to work and continues to enjoy painfree coitus. Bone density studies repeated after 12 months of treatment confirm that her BMD has been maintained. The pretreatment L2–L4 BMD was 1·127 g/cm^2, left femoral neck BMD 0·990 g/cm^2, post-treatment values were 1·172 g/cm^2 and 1·017 g/cm^2 respectively, representing an increase of 4% in lumbar spine and 3% in the femoral neck. The precision error with this equipment (DEXA; Lunar DPXL) is 2% for the lumbar spine and 3% for the femoral neck, thus there has probably been a small incrase in BMD in our patient.

Discussion

Severe pelvic endometriosis poses a difficult management problem, particularly if the patient wishes to retain her fertility. Radical surgery remains the only definitive treatment for such extensive disease (West 1990) and conventional medical treatment offers, at best, only short term suppression of the condition and its symptoms.

The use of danazol and progestogens is limited by undesirable physical, psychological and metabolic side-effects (Buttram *et al.* 1982). Our patient both failed to gain relief with such medication and experienced unpleasant side-effects.

Suppression of ovarian function by pharmacological means

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i.e., a reversible 'medical oophorectomy', offers an attractive alternative in this difficult situation. The potential of such therapy was soon grasped (Lemay & Quesnel 1982; Shaw 1983; Lemay *et al.* 1984) and convincing reports of endometriosis responding well to GnRH analogues led to controlled trials (Matta & Shaw 1987; Dmowski *et al.* 1989). These indicated both an improved response of the endometriosis and less troublesome side effects when the GnRH agonist buserelin was compared with danazol.

The early optimism for this approach has been tempered particularly by the loss of bone mass (Matta & Shaw 1987; Fraser 1988). This has been reported to be as high as 8·2% after 6 months of GnRH analogue therapy (Dodin *et al.* 1991). Unpleasant symptoms of flushing, vaginal dryness and dyspareunia created by the hypo-oestrogenic state (Shaw 1988) also limit compliance. The bone loss, fortunately, appears to reverse spontaneously when treatment stops (Waibel-Treber *et al.* 1989). There is evidence that adding a progestogen to GnRH analogue therapy may spare bone loss and reduce side-effects (Surrey *et al.* 1990; Riis 1990), but oestrogenic supplementation is probably essential to maintain vaginal health and protect the cardiovascular system.

The addition of a small daily dose of oestrogen and continuous progestogen to GnRH treatment may be an effective way of preventing both loss of bone and hypo-oestrogenic symptoms yet maintaining endometrial atrophy and amenorrhoea (Magos *et al.* 1985). The efficacy of 'continuous combined' HRT is proven in post-menopausal women (Cust *et al.* 1990) and 0·625 mg of conjugated oestrogens has been shown to be a bone conserving dose (Stevenson *et al.* 1990). Hormone replacement therapy could make GnRH analogue therapy safer and more acceptable in the treatment of a wide range of gynaecological conditions. However, the high cost and lack of long term safety data are likely to limit its use for the time being.

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Received 28 October 1991
Accepted 28 November 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 345–347

Incarceration of a bicornuate retroverted gravid uterus presenting with bilateral ureteric obstruction

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Case Report

A 19-year-old primigravida, with no significant past medical history, booked at 14 weeks gestation. Her blood pressure was 140/70 mmHg and she had no proteinuria. A routine vaginal examination confirmed the uterine size and revealed no abnormality. An ultrasound scan at 18 weeks showed a normal singleton pregnancy and confirmed the length of gestation. At 30 weeks gestation her blood pressure was recorded at 180/90 mmHg and there was marked oedema of her feet, therefore she was admitted to hospital. Initially her diastolic blood pressure settled to 80–85 mmHg and her urine remained free of protein. Blood tests were as follows: haemoglobin 9·4 g/dl (normal red cell indices), haematocrit 0·27, white cell count 7·9 $\times 10^9$/l, platelets 222 $\times 10^9$/l, urea 5·3 mmol/l, creatinine 119 µmol/l and urate 0·42 mmol/l.

An ultrasound scan of the maternal kidneys revealed gross hydronephrosis, worse on the right, with dilatation of the upper right ureter. Further renal investigations included negative microscopy and culture of a mid-stream urine specimen, creatinine clearance of 58 ml/min and 24 h urinary protein excretion of 0·21 g.

Over the following week her serum creatinine rose to 153 µmol/l, the plasma urate increased to 0·47 mmol/l and the creatinine clearance fell to 46 ml/min. She remained asymptomatic but as her diastolic blood pressure increased to 90–100 mmHg she was treated with labetalol, 100 mg twice daily.

Ultrasound measurements of the fetal biparietal diameter, abdominal circumference and amniotic fluid volume were normal. The maternal condition stabilized and the pregnancy was allowed to continue with further careful observation. At 34 weeks gestation the creatinine clearance fell to 24 ml/min. Other investigations at that time included a normal full blood count, urea 8·6 mmol/l, creatinine 267 µmol/l and urate 0·56 mmol/l. Ultrasound had continued to show satisfactory fetal growth. The fetus was presenting by the head of which four fifths was palpable abdominally. It was decided to deliver the patient by caesarean section.

A Pfannenstiel incision was made and the bladder and uterovesical peritoneum were deflected inferiorly with considerable difficulty, resulting in slight damage to the bladder. What appeared to be the lower segment was then incised but instead of the uterine cavity being entered a second uterine surface was encountered. The anatomy was unclear although the fetal head could be felt within the underlying uterine muscle, therefore a second transverse incision was made and the amniotic cavity was entered. A live female infant, birthweight 2·48 kg, was born with the aid of Wrigleys forceps and the Apgar scores were 4, 9 and 10 at 1 min, 5 min and 10 min, respectively.

Careful examination of the abdominal organs revealed that the uterus had been acutely retroverted, with the fundus lying in the pouch of Douglas (Fig. 1). Hence the presentation was breech (by definition) but had appeared to be cephalic. There was an 8 cm diameter mass at the right cornu of the uterus. It looked like a fibroid but was covered with a very unusual vascular pattern, and seemed to be the cause of the retroversion. The right fallopian tube was also attached at this point. Both ureters were found to be of normal diameter below the pelvic brim, indicating that the compression had occurred at the brim.

The initial incisions had been through the anterior and posterior walls of the vault of the vagina, which was stretched by the uterus behind, so that the uterus was completely detached at that point. The displaced posterior surface of the uterine fundus had been incised transversely and the baby was born through this and the vaginal incisions. The uterine blood vessels were intact.

It was decided to proceed with a hysterectomy, conserving both ovaries, since the integrity of the suture lines could not be guaranteed and the nature of the uterine mass was uncertain. The bladder was repaired and a catheter was left in situ, on free drainage, for 10 days. The puerperium was essentially normal with a gradual return of renal function to normal.

Pathological and histological examination revaled that the uterus was bicornuate, the right lateral mass being a rudimentary horn. There was no evidence of any tumour.

Discussion

Retroversion of the uterus is present in 15% of pregnancies during the first trimester (Greenhill 1965), but the fundus will usually enter the abdominal cavity as the uterus enlarges, with no resulting complications. Retroversion will persist and the fundus will become incarcerated in approximately 1 in 3000 pregnancies. As in the nine patients reported by Gibbons & Paley (1969), these will usually present between 12 and 20 weeks gestation with urinary problems or lower abdominal pain. If miscarriage does not occur it may be possible to reduce the uterus to its normal position, enabling normal delivery.

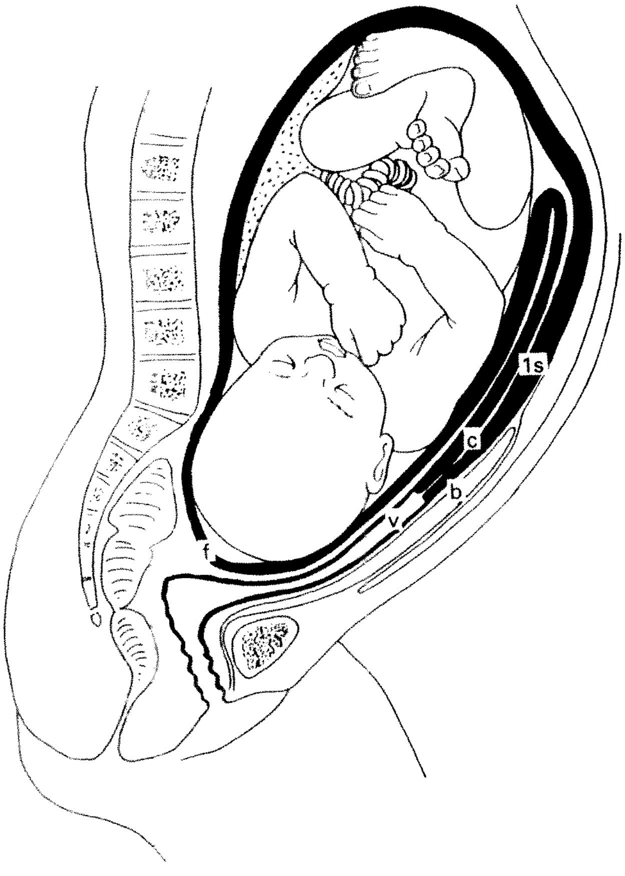

Fig. 1. Diagram (median sagittal section) showing the anatomical configuration of the incarcerated retroverted gravid uterus.

(b) bladder; (c) cervix; (f) displaced uterine fundus; (ls) lower uterine segment; (v) vagina.

Smith *et al.* (1962) reported a case of anterior sacculation of the pregnant uterus at term. They drew attention to what was called true sacculation as opposed to pseudo-sacculation, pointing out that this distinction has important implications for delivery. Evans *et al.* (1986) suggested that the case described by Smith *et al.* (1962) would better have been termed retroversion with incarceration, since it represented complete retroflexion with the lower uterine segment stretched anteriorly over the uterine surface and the fundus situated in the pelvis. With this situation vaginal delivery is possible and if labour occurs there is a danger of uterine rupture (Evans *et al.* 1986).

The term sacculation would better be reserved for cases in which part of the wall of the uterus has ballooned out but uterine polarity remains normal. This condition was reviewed by Weissberg *et al.* (1972) and a normal vaginal delivery was achieved in 10 of the 38 cases reported.

By these definitions, incarceration of the retroverted gravid uterus persisting beyond the second trimester has been reported only six times since 1806 (Merriman 1806; Oldham 1860; Murray 1934; Smith *et al.* 1962; Wood 1967; Evans *et al.* 1986). Its occurrence is associated with adhesions between the fundus and the pouch of Douglas, a fundal fibroid, uterine malformation or a deep sacral concavity with overlying sacral promontory. This is the third case associated with a bicornuate uterus and the second with bilateral hydronephrosis (the other case associated with hydronephrosis was also associated with a fundal fibroid).

When a pregnancy is complicated by bilateral hydronephrosis an obstructing pelvic lesion must be considered and a vaginal examination should be done. In this case the vaginal examination at booking had been normal and subsequent ultrasound scans had not raised further suspicion of a pelvic mass. However, vaginal examination should have been repeated, in which case a mass in the pouch of Douglas would have been identified and it would have proved difficult to palpate the cervical os. These findings should have suggested retroverted incarceration. Had the diagnosis still remained obscure, then a midline laparotomy incision would have been made to provide adequate access to whatever pathology might have been encountered. It may then have been possible to correct the polarity of the uterus, as described by Evans *et al.* (1986), enter the uterine cavity via an appropriate incision, and obviate the need for hysterectomy.

We doubt the reliability of ultrasound for diagnosing the condition described. Given that a pelvic mass has been identified it would help to distinguish a fibroid from a cyst, but the thin layers of the attenuated lower segment stretched anteriorly would, to the unsuspecting observer, appear to be layers of the anterior abdominal wall.

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Received 1 August 1991
Accepted 10 October 1991

British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 347–348

The teratogenic effects of undiagnosed maternal hyperphenylalaninaemia: a case for prevention?

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Case reports

Patient 1

This woman was born in 1956. In 1986 she was referred for genetic counselling on account of having had two children with mental handicap. Her obstetric history also included one second trimester and two first trimester miscarriages. Her affected children, born at term, had low birthweights of 2·3 kg and 2·4 kg respectively. Her past medical history was unremarkable but her educational history revealed low attainment and a requirement for remedial teaching at school. Her mentally handicapped children were non-dysmorphic with head circumferences of −2 SD and −1 SD respectively. Investigations on the children seeking a cause for their mental handicap were unrevealing but investigation of the mother revealed a fasting plasma phenylalanine level of 1247 μmol/l and chromatographic examination of her urine confirmed phenylketonuria.

Patient 2

This woman was born in 1959. She had one first trimester miscarriage during 1979 and a second in 1989 before giving birth at term to a microcephalic female infant who weighed 2·6 kg. The parents were referred for genetic counselling on account of their infant's microcephaly (OFC –4 SD) and congenital heart defect which was diagnosed as a ventricular septal defect. The mother revealed that she herself had required remedial education (measured IQ 67) and had been treated in hospital during her early childhood for a disorder beginning with the letter "p". It transpired that her own mother, on learning of the referral to the genetic counselling clinic, had told her daughter to mention this episode of hospital treatment in case her grandchild's condition was related. Given this information, the mother's plasma phenylalanine level was measured at the genetic clinic and was 1466 μmol/l. Subsequent examination of records stored on microfiche at the regional paediatric hospital confirmed phenylketonuria had been diagnosed in 1961 when the mother was age 2 years, after her presentation with delayed development. Although the family doctor was then informed that dietary therapy should continue 'indefinitely' it was probably abandoned within one year and the family was subsequently lost to hospital follow-up.

Discussion

These case histories serve to remind that maternal phenylketonuria may go undiagnosed until the birth of a baby who is severely handicapped by the teratogenic effect of the maternal condition (Levy & Waisbren 1983; Appleton *et al.* 1984). Important additional clues to this diagnosis are the histories of recurrent miscarriage (Stevenson & Huntley 1967), the mothers' intellectual impairment and their ages—both mothers were born before the start of neonatal screening for phenylketonuria which began in the UK during the mid 1960s. The newborn screening programme has been very effective since its inception (Smith *et al.* 1991). Accordingly, it is to be expected that the number of undiagnosed women will decline as the population, born before the start of screening, ages. Presently the National Phenylketonuria Register facilitates follow-up of diagnosed cases and if this is near complete and all affected women are counselled that they must return to a strict diet before they become pregnant, then the teratogenic effect of the disease should decline. However, our experience and that of others indicates a significant number of known affected women do not return to a phenylalanine-restricted diet before conception. (Scriver *et al.* 1989). There are probably many complex reasons to account for this, but avoidable factors, illustrated by the experience of our second patient who had been diagnosed in childhood, includes poor communication between medical colleagues together with failure to appreciate the damaging effects of maternal hyperphenylalaninaemia. Various strategies have therefore been proposed to prevent the teratogenic effect of untreated maternal phenylketonuria and hyperphenylalaninaemia (Luder & Greene 1989). These range from non-selective screening of all pregnant women to selective screening of those with a history of miscarriage or the birth of a typically damaged infant. Although it seems wasteful to repeat in adult life a screening test which will, in nearly all cases, have been performed at birth, our experience of identifying by chance two affected mothers in the past 5 years shows that re-screening proposals merit detailed consideration.

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Received 16 October 1991
Accepted 26 November 1991

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British Journal of Obstetrics and Gynaecology
April 1992, Vol. 99, pp. 349–352

CORRESPONDENCE

Insufficient remodelling of the uterine connective tissue in women with protracted labour

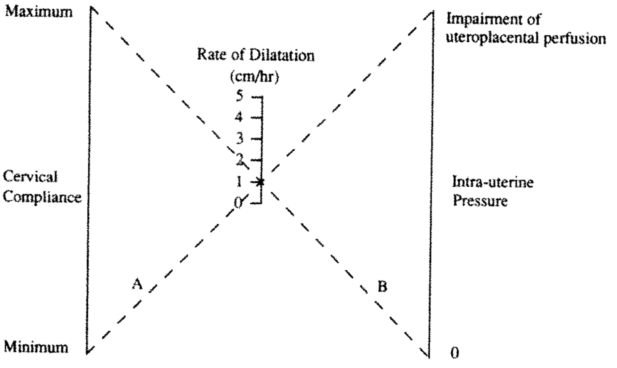
Dear Sir,

We found the study by Granström *et al.* (1991) of great interest. While obstetricians have become accustomed to using the cervix as an indicator of the progress of labour, few would look further to pose questions regarding the mechanisms by which change is mediated or to what effect the cervix itself has on the process of labour. This study addresses the first of these problems.

During pregnancy, the cervix must remain as a firm tubular structure to retain the conceptus, and its tightly wound, inelastic, circumferentially arranged collagen fibres are ideally suited to this purpose. During labour the role is reversed. The cervix needs to dilate, yet its architecture must remain intact for future pregnancy. The collagen fibres are embedded in a glycocoprotein ground substance and the interaction between ground substance and collagen determines the ability of the cervix to deform, i.e., to efface and dilate (Uldbjerg 1989). The data presented are the first to our knowledge which link directly the physicochemical state of the cervix to labour outcome. Most clinicians are now aware of the beneficial effects of ripening the cervix at the time of labour induction and the value of prostaglandins. However, the logical conclusion of these findings is to extend the cervical influence to the interpretation of abnormalities of labour itself.

Our own work would support the hypothesis that 'cervical dysfunction' may contribute to slow progress of labour and addresses the second of the two questions mentioned earlier.

Poor cervical progress is not always the result of poor uterine activity and may even be associated with levels of uterine activity that would be considered above the normal range (Gee & Beazley 1980). Earlier studies have shown that an unfavourable cervix (a low Bishop's score) is associated with slow progress and the development of high intrauterine pressures (Gee 1983). Intrauterine pressure generation depends upon the development of tension within the wall of the uterus due to muscle contraction. However, in addition to muscle, the uterine wall contains 'elastic' elements (Coren & Csapo 1963). Little attention has been paid to the effects of these 'passive' elements on the function of the myometrium and the development of wall tension. The collagenous cervix makes up part of the uterine wall. Its compliance will down-modulate the tension developed by the myometrium, such that the greater its compliance the less the tension and the weaker the perceived contraction. The converse will also be true, the non-compliant cervix failing to modulate increases in uterine wall tension resulting in a rapid rise in intrauterine pressure and higher peak pressures. These effects may be demonstrated by computer modelling (Gee *et al.* 1988). Thus, when the cervix is non-compliant, progress is poor and high intrauterine pressures are generated. Further stimulation would be dangerous, and the pressures generated would quickly reach the threshold above which blood flow through the placenta is impaired resulting in fetal distress (Janbu & Neishein 1987; Borell *et al.* 1964). This is illustrated by the nomogram in Fig. 1. A rate of cervical dilatation of 1 cm/h may be achieved by either increasing the compliance of the cervix (line A), or by increasing uterine wall tension and hence pressure (line B). This may result in impairment of uteroplacental blood flow resulting in fetal distress, a common accompanying feature in women delivered by caesarean section for 'failure to progress'.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Cervical Compliance
Minimum
Rate of Dilatation (cm/hr)
5
4
3
2
1
0
A
B
Impairment of uteroplacental perfusion
Intra-uterine Pressure
0

Fig. 1. Labour nomogram.

The corollary of poor cervical preparation is preterm cervical ripening resulting in preterm delivery. High compliance of the cervix would permit rapid effacement and dilatation with apparently little appreciation of uterine activity (Pearce 1986). Perhaps these considerations go a long way to explaining why tocolytics, which only affect the myometrium, have had little impact on preventing preterm delivery (Oláh & Gee 1992).

Other labour conditions may also be attributed to the cervical state. Women having precipitate deliveries may have low uterine activity (Crawford 1975; Gee 1982).

Our recent studies have attempted to validate the clinical observations made. Measurements of uterine activity gives only one side of a complex equation. Using a cervimeter (Richardson *et al.* 1978) to continuously record the cervical response to myometrial activity, we have been exploring the possibility of defining the visco-elastic response of the cervix *in vivo*. The visco-elastic properties are dependent on the biochemistry of the cervix. In labours that progress rapidly we have shown that dilatation of the cervix may begin before the generation of intrauterine pressure (Oláh *et al.* 1991). We interpret this as a compliant cervix modulating uterine wall tension to such a degree that the initial part of myometrial activity is cancelled out. Only when the collagen fibres are loaded is tension and pressure produced. The biochemical data presented by Granström *et al.* (1991) in conjunction with the predictions of the computer model (Gee *et al.* 1988) is crucial to our understanding of these observations and reinforces the view expressed above with regard to preterm labour.

The message we would like to convey, taking into consideration the biochemical data presented here and the physical data currently being collected by ourselves, is that there should be a shift away from relating labour pathology to myometrial activity. The critical role of the cervix must be acknowledged. It is our belief that the solutions to some intrapartum problems and preterm labour lie with a better understanding of the physicochemical nature of the cervix.

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Early postoperative mortality following hysterectomy. A Danish population based study, 1977–1981

Dear Sir,

In a recent article examining early postoperative mortality after simple hysterectomy (Loft *et al.* 1991), the authors found that, as compared to age-matched women in the general population, women undergoing simple hysterectomy had an increased relative risk (RR) of death from cardiovascular disease (RR = 7·18, $P<0{\cdot}001$). Although this was in accord with a review of the literature (Centerwall 1981), the authors appear uncertain what to make of this, since the relative risk of death from all other causes was similarly elevated (RR = 5·40, $P<0{\cdot}001$). This apparent difficulty is caused by two conceptual errors: (i) the authors use too broad a definition of cardiovascular disease, and (ii) they fail to take into account expectable causes of death attributable to abdominal surgery, both immediate mortality and short-term.

A review of the literature indicates that simple hysterectomy is a risk factor for subsequent coronary heart disease (CHD) rather than for other cardiovascular events such as embolism/thrombophlebitis and apoplexy (Centerwall 1981). In contrast, deaths from embolism/thrombophlebitis are a recognized complication of hysterectomies, as are deaths from pneumonia, ileus and infection; not surprisingly, deaths from these causes occurred 15 times more frequently in the hysterectomy group than in the reference population (Loft *et al.* 1991). Deaths due to complications of the operation itself occurred, by definition, only in the hysterectomy group. If we recalculate, then, we find 18 deaths due to coronary heart disease in the hysterectomy group, where only four were expected (RR = 4·35, $P<0{\cdot}05$). If we then exclude deaths which are expectably attributable to the immediate and short-term complications of abdominal surgery (i.e., surgical complications, embolism/thrombophlebitis, pneumonia, ileus, and infection), we are left with a residual category of nine non-CHD deaths in the hysterectomy group where six were expected—not a significant difference. Thus, excluding complications of abdominal surgery *per se*, the elevated risk of mortality among hysterectomy patients is confined to coronary heart disease. If the data were re-analysed, it would be expected that excess mortality in the premenopausal women was primarily attributable to CHD, whereas the excess mortality in the postmenopausal women was primarily attributable to complications of the operation, both immediate and short-term.

Ideally, one would match women undergoing hysterectomy with women undergoing a similar operation, but without hysterectomy. Such a study has been conducted in Finland, where 90 premenopausal women undergoing hysterectomies for uterine myomas were paired with 90 women undergoing uterine myomectomies, matched for age, parity, height/weight ratio, and year of operation (Punnonen *et al.* 1987). The subsequent risk of new-onset CHD was five times greater in the hysterectomy group than in the matched myomectomy group ($P<0{\cdot}05$). The elevated rate of CHD among premenopausal women with simple hysterectomies could not be explained by differences in smoking or use of oestrogens.

By what mechanisms can a simple hysterectomy in a premenopausal woman lead to an increased risk for CHD? On the one hand, the uterus may have an endocrine function, the elimination of which promotes heart disease, either directly or through failure of the ovaries (Siddle *et al.* 1987). This hypothesis has gained plausibility since we learned that the uterus elaborates prostaglandins. On the other hand, the procedure itself may compromise blood circulation to the ovaries, leading to premature ovarian failure. It is well-documented that a substantial proportion of premenopausal women undergoing simple hysterectomy suffer premature ovarian failure (Siddle *et al.* 1987; Kaiser *et al.* 1989). The two hypotheses are not mutually exclusive. The Danish findings (Loft *et al.* 1991) reinforce the need to consider CHD as one of the potential consequences of 'simple' hysterectomy.

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Author's reply

Dear Sir,

We welcome the opportunity to comment on the remarks and suggestions made by Dr Centerwall.

Dr Centerwall first argues that we used too broad a definition of cardiovascular diseases since, according to him, the outcome of interest is coronary heart disease (CHD). With reference to the literature Dr Centerwall points out that simple hysterectomy may be considered a risk factor for CHD rather than for cardiovascular disease in general. However, the development of atherosclerosis is a lengthy process and all the references he cites are based on relatively long periods of observations—typically years rather than a single month. However, since we studied short term mortality we feel justified in focusing on mortality due to cardiovascular diseases in general.

Dr Centerwall also suggests that it would be relevant to exclude all causes of death that may be attributable to abdominal surgery, both immediate and short-term mortality (surgical complications, embolism/thrombophlebitis, pneumonia, ileus and infections). After these proposed exclusion we are left with a 'residual category of non-CHD deaths' to which Dr Centerwall is devoting his interest.

However, these 'complications' include a number of causes of death which are also relatively common in the population reference sample. Consequently we do not find it clinically relevant to exclude all of them from the comparison. Because we find the category of 'complications' suggested by Dr Centerwall to be too broad, we have applied a more restrictive definition i.e., diagnoses indicating immediate complications due to the surgery itself. After excluding this set of complications we are left with an alternative residual category we refer to as non-CHDa.

Finally Dr Centerwall suggests that mortality among premenopausal women is attributable primarily to CHD, while operative complications are more important among postmenopausal women.

We have reanalysed our data to see how the suggested reclassification and assumptions might influence the results. Adjusting for age differences a comparison of the suggested categories gives the following results (Mantel-Haenszel test and estimation):

The first non-CHD category is defined as suggested by Dr Centerwall, and the results (adjusting for age) confirm his crude calculations. However, as seen from the Table, there is a highly significant difference in non-CHD mortality when only complications in the narrow sense are excluded, residual category non-CHDa.

While the data clearly show an increased occurrence of CHD in the first month following hysterectomy we do not feel convinced that this is a consequence of 'simple' hysterectomy. On the contrary this result might well support the alternative interpretation: Somehow patients selected for hysterectomy are at high risk for CHD even before the operation. Hysterectomy may trigger the mortal event without causing the underlying disease. Any major abdominal surgery, however, might have this effect.

Turning to the relation of age to cause of death, Dr Centerwall suggests specific patterns of mortality for pre- and postmenopausal women.

Table 2 gives the absolute numbers of deaths among hysterectomy patients by age and cause of death.

Whereas Dr Centerwall suggests that CHD is the primary cause of the excess mortality among premenopausal women, no such deaths occurred among Danish hysterectomy patients. Among postmenopausal women, however, CHD and complications in the broad sense account for similar numbers of deaths.

We agree that the occurrence of deaths due to coronary heart disease is a very important issue in relation to hysterectomy, but primarily in the long term.

Table 1. Post hysterectomy mortality from coronary heart disease (CHD)

Category	Relative risk	χ^2	*P*
CHD	7·53	52·63	<0·00001
non-CHD	2·35	3·58	<0·10
non-CHDa	4·95	40·90	<0·00001

Table 2. Number of deaths among hysterectomy patients

		Cause of death	
Age (years)	*n*	CHD	Compl.*
<50	21 477	0	6
50+	7 715	18	14

*Complications according to Dr Centerwalls's definition.

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Fish-oil and pre-eclampsia

Dear Sir,

In a series of letters to the Editor (*BJOG* (1991) **98**, 737–743), Drs Broughton-Pipkin, Secher *et al.* and McCormack & Constantine have commented on possible adverse effects of the dietary intake of fish-oils during pregnancy. We would like to add our comments based upon our, albeit, limited experiences (25 women) of using both fish-oil triglyceride concentrates (Maxepa), and mixtures of omega-3 acid ethyl esters during, and before, pregnancy.

We agree with McCormack & Constantine (1991) that the preparations of omega-3 fatty acids used are important in terms of patient compliance, vitamin A toxicity, and urate levels, as well as having direct relevance to the actual dosages of omega-3 levels being ingested—hence we are now using ethyl-esters rather than triglyceride formulations of omega-3 fatty acids in our ongoing trials.

Whilst using Maxepa and Himega, and a laboratory ethyl-ester formulation, in doses up to 3 g equivalents of eicosapentaenoic acid per day (5 g total omega-3 acids daily), in pilot, and now double-blind therapeutic trials for chronic and gestational induced hypertension, and some patients with antiphospholipid syndrome, we have not observed significant changes in haematology and biochemistry due to treatment (Starling *et al.* 1990). More specifically we have not observed changes in bleeding time, platelet count, or uric acid, other than those which normally occur during pregnancy.

These preliminary results are in keeping with the findings of Secher *et al.* (1991) and do not support the concerns of Broughton-Pipkin (1991). It is perhaps worth noting that some of our patients have had histories of previous thrombotic events. In such cases the antithrombotic effects of omega-3 fatty acids could well lead to platelet preservation off-setting platelet consumption. In a few instances where the placenta, or placental bed biopsies, have been examined histologically in patients with antiphospholipid syndrome and hypertension who are taking fish-oils, there has been no evidence of thrombosis.

We concur with McCormack & Constantine (1991) that high doses of Maxepa can cause unacceptable belching and unpleasant fish-oil taste and we suggest that using ethyl-ester derivatives can reduce these problems to tolerable levels. The only adverse effects we have experienced are occasional stomach cramps, and diarrhoea at the start of therapy. Both side-effects appear, in most instances, to be dose-related and are overcome by the incremental introduction of the therapy over several days.

Finally our limited experiences indicate that the monitoring of compliance is more reliably achieved by regular monitoring of erythrocyte membrane fatty acid profiles, rather than by patient questionnaires. In view of the potential effects of omega-3 fatty acids on fetal growth (Olsen *et al.* 1990) we are of the opinion that future studies need to monitor the fetus by means of ultrasound during pregnancy as well as checking maternal and fetal outcome.

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BOOK REVIEWS

Gamete Interaction: Prospects for Immunocontraception. Proceedings of the Third Contraceptive Research Development edited by Nancy J. Alexander, David Griffin, Jeffrey M. Spieler & Geoffrey M. H. Waites. Wiley-Liss New York, Chichester, 1991, 651 pages, with figures and tables £93.50

A contraceptive vaccine would revolutionize fertility control, especially in the developing world, where a successful model already exists in the infectious disease control programmes. A vaccine is easy to administer and should ensure long-term but finite contraception at low cost. This was recognized three decades ago, several agencies primarily the WHO, embarked on a search for such a vaccine. The WHO concentrated on developing an anti-HCG vaccine. More recently research into anti-gamete vaccine has been stepped-up as an alternative in case anti-hormone vaccines prove ineffective or ethically/politically unacceptable. Moreover, anti-gamete vaccines have the potential for use by men as well as women.

In November 1989 the WHO and CONRAD (Contraceptive Research and Development Programme) invited 43 experts from 27 countries for a workshop to evaluate progress in identifying 'leads' for further research. The proceedings of this workshop provide a fascinating chronology of the painstaking and meticulous construction of a complex jigsaw in which several pieces still have to be found.

So far many 'target events' have been identified such as sperm maturation, the acrosome reaction, sperm/zona pellucida binding and in the case of anti-HCG vaccines the early implantation phase. Many of these possibilities have not been investigated in the human.

The evidence presented suggests that the anti-hCG vaccine works through a luteolytic effect that prevents implantation. Data, so far, seem to indicate that the vaccine blocks fertility with no discernible alteration in the menstrual cycle.

The question of which gamete immunogen to target with an anti-gamete vaccine is more elusive. Several sperm surface antigens, epididymal proteins and zona pellucida components have been identified. The various authors try to clarify the complex issues of adjuvants and vehicles required to maintain high titres of antibodies for long periods of time. I was fascinated by the work on epididymal function that leads to the conclusion that fertilization is indeed the culmination of mechanisms that start in the testicular tissue. It is also interesting that to follow leads from natural subfertility caused by auto-immune mechanisms has not been rewarding.

What progress has been made so far? The production of specific gamete antigens by recombinant DNA technology has been a recent focus of interest, while work with monoclonal antibodies against gamete antigens continues. Assessing efficacy in primate models is at last happening. Several safety and efficacy issues remain to be addressed. Sperm antibodies have to be available in the genital tract at sustained high concentrations to be effective. Epitops that are prime targets for research are ones that appear last in oocyte development so that antibodies against them would spare the immature ovarian follicles. the vaccine needs to be completely reversible within a designated period (probably two years) and an easy and relaible test must be found to predict effectiveness.

Long-term safety of a vaccine which may need to be administered at frequent intervals over the fertile lifespan of the individual is obviously essential. As pointed out by one of the authors, the two areas of biomedical research where liability insurance is particularly difficult and expensive to obtain are vaccines and contraception! With this in mind those working in this field of immunocontraception must be applauded and supported.

Though gamete interaction is a 'special interest' subject, it is relevant to both contraception and subfertility. None of the chapters is too long or too technical to be off-putting. The interested reader may find this book, or sections therein useful as a reference and to elucidate the scientific basis whenever another milestone in this fascinating journey is arrived at.

Ali Kubba

Achievements in Gynecology 1989–90 (Contributions to Gynecology and Obstetrics Vol. 18), edited by S. Mancuso. Karger, Basel 1991, 186 pages, Sw Fr 180, DM 216, £78.00, US $144

The fourteen chapters in this volume are based on presentations of (I assume) invited speakers to the Department of Gynecology and Obstetrics at the Catholic University of Rome over a two year period. Of the 14 chapters, eight are written by Americans, four by Italians with one Spanish and one Swedish contribution. Hardly a representative international authorship, more a collection of papers by old friends and touring lecturers!

This, of course, does not necessarily devalue the contributions but does, I suspect, explain the mixture of topics that have been included. The authorship is distinguished but the subject index is so disparate that I cannot ascertain who the target readership for this book might be. MRCOG candidates would devour the statistics about world health in the chapter by Diczfalusy, which contains United Nations and World Health Organization population and health projections, but I suspect that most clinicians would not take too much time to read the chapter entitled 'Antigenic changes of cancer cells induced by triazine compounds'.

Similarly, although the review chapter on the role of operative gynaecological endoscopy may be irrelevant to a biochemist, the chapter on the carcinogenic consequences of DNA alkylation makes fascinating reading.

The chapter on the improvement of cytodiagnosis of ovarian tumours using monoclonal antibodies reads very much like an article in a mainstream clinical journal, whereas that on 'The apparent paradox of sexual differentiation of the brain' would clearly be confined to a more esoteric publication. In spite of these observations, in general, the chapters are well written and the review articles about viruses and cervical carcinoma, the pitfalls of cervical cancer screening and induction of ovulation in polycystic ovary syndrome contain interest for obstetricians and gynaecologists of all grades.

There are one or two instances of poorly written English. For example, the statement 'beverage source has been implicated as a distinct risk factor (in the aetiology of fetal alcohol syndrome) in several . . . studies'. Does this 'source' refer to the country of origin of the alcohol drink, whether the brew is consumed in a bar or bought in an off licence or whether the drink is bought for you by a colleague or you drink alone. Unfortunately, further reading does not resolve the uncertainty.

The fact that this is the 18th volume of the series 'Contributions to Gynecology and Obstetrics' must indicate that this is, at least from the publisher's point of view, a successful venture. However, I cannot believe that anyone would purchase it for private use because of the varied nature of the subjects and depth of knowledge required to benefit from their reading. I am sure, however, that it will be fairly extensively borrowed from a Medical School Library by members of the Department of Obstetrics and Gynaecology as well as many laboratory based and experimental departments. This is not a book to browse through, however, and once the article of interest had been looked at, the book would, I imagine, be returned to the library with the other chapters unread.

Frank Lawton

Abortion and Afterwards by Vanessa Davies. Ashgrove Press, Bath, 1991, 226 pages, £6.99 paperback

Hard personal experience can lead to a biased view but Vanessa Davies has used the distress she experienced from an unwanted pregnancy and abortion to produce a book that is just what other women in this position need. Some chapters provide information on pregnancy, services and the practical aspects of abortion but the strength of the book is in the chapters dealing with choice, decision making, feelings, grief, and the effect of abortion on a relationship. Particularly effective use is made of extracts from the account of individual women of their own experience.

The medical information about abortion is adequate but would have had more precise detail if the author had had the text checked by a gynaecologist before going to press. More information about the size and development of the fetus would have given women greater insight into the technical ease of early and the difficulties of late abortion. There is a need for a fuller perspective on post abortion complications. These problems involve only a small part of the book and could be corrected easily in a further edition. There should be further editions because there is no other paperback that provides so much help for a woman considering whether she should have an abortion or who needs to come to terms with having had an abortion.

David Paintin

Progress in Obstetrics and Gynaecology Volume 9 edited by John Studd. Churchill Livingstone, Edinburgh, London, 1991, 420 pages, with figures and tables, £24.95

Yet again John Studd has produced a timely collection of pertinent obstetrical and gynaecological topics for perusal and learning. Doppler, aspirin, fertilization by micro invasion, endometrial ablation are all covered in an effort to keep us informed of recent developments and weighty intelligent reviews of old kernels like hypertension, massive obstetric haemorrhage, hirsutism and medical treatment of menorrhagia. I especially like the chapter on pre-labour, spontaneous rupture of membranes, if only for the fact that it is so poorly dealt with in traditional text books. Studd has carefully selected the authors of the chapters for their recognized interest in their particular subject. This ninth volume is a must for all those with an interest in postgraduate and continuing education in obstetrics and gynaecology.

James C. Dornan

Clinical Gynaecological Oncology Second edition edited by John H. Shepherd and John M. Monaghan. Blackwell Scientific Publications, Oxford, 1990, 479 pages, with figures and tables, £59.50

The fundamental difference between the second and first editions of this popular text is that all the authors are now based in the UK. This is therefore one of very few books on gynaecological oncology which truly reflect practice in this country. The chapters have been brought up to date as a result of experience since the first edition was published in 1985.

The text remains eminently readable and will prove useful to both undergraduates and graduates alike, and especially those gynaecologists seeking a knowledge of current British gynaecological cancer management in preparation for the MRCOG examination.

Ian Duncan

Books received some of which will be reviewed at a later date

A Text and Atlas of Intergrated Colposcopy by Malcom Anderson, Joe Jordan, Anne Morse & Frank Sharp. Chapman & Hall Medical, London, 1992, 235 pages, fully illustrated with coloured plates, £70.00

Current Obstetric Medicine Volume 1 edited by R. V. Lee, W. M. Barron, D. B. Cotton & D. Coustan. Mosby Year Book, St Louis, Baltimore, 1992, 380 pages, £48.00

Polycystic Ovary Syndrome. (Current Issues in Endocrinology and Metabolism) edited by Andrea Dunaif, James R. Givens, Florence P. Haseltine & George R. Merriam. Blackwell Scientific Publications, Oxford, London. Boston 1992, 392 pages with figures and tables, £69.50

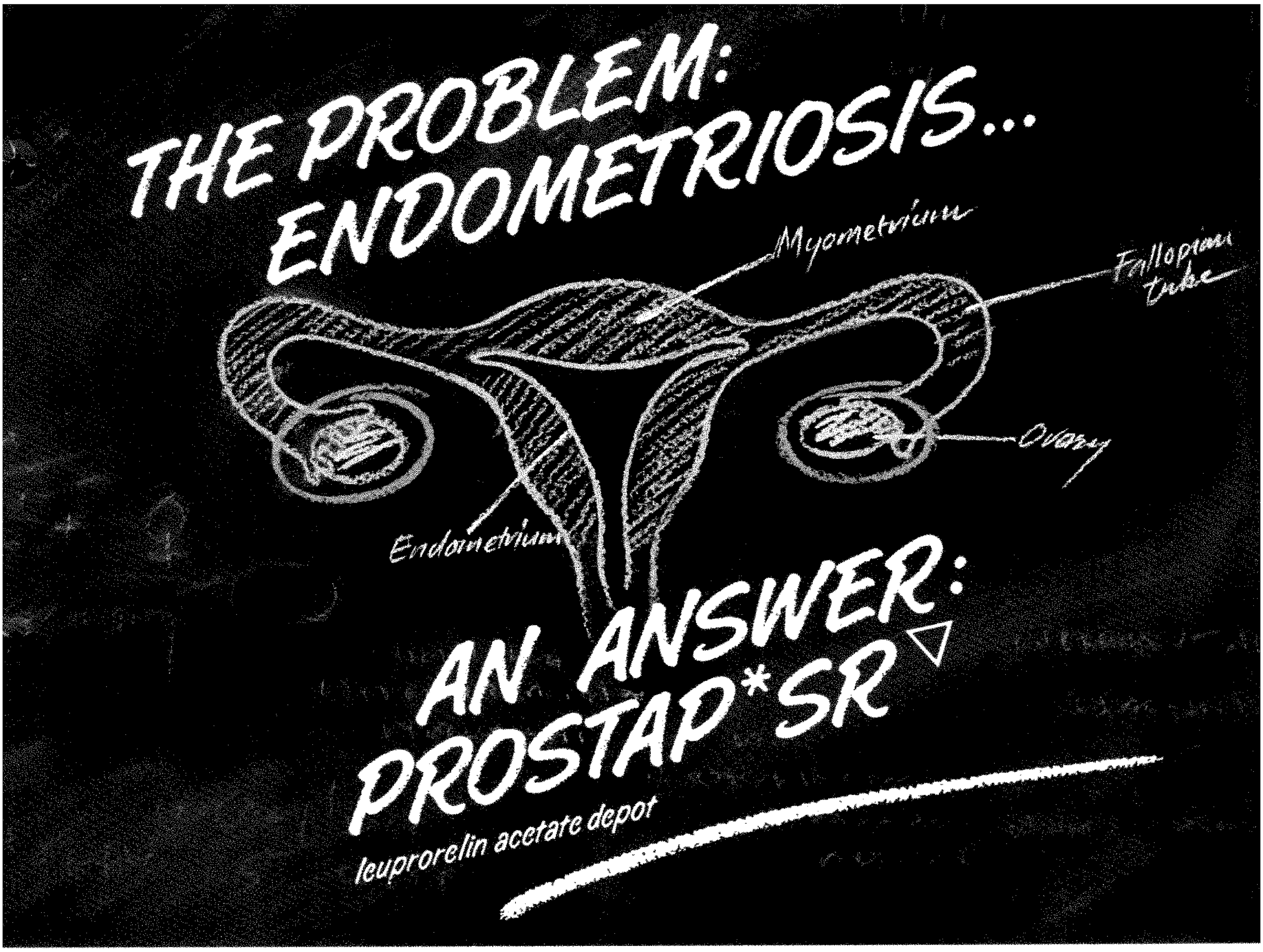
ABC of Antenatal Care by Geoffrey Chamberlain. British Medical Journal Publication, London 1992, 84 pages, fully illustrated, UK £9.95, Overseas £12.00

Diagnostic Imaging in Infertility, second edition, by Alan C. Winfield & Anne Colston Wentz, Williams & Wilkins, Baltimore, 1992, 312 pages, fully illustrated, £65.00

Management of Patients and Sexually Transmitted Diseases Report of a WHO Study Group. Technical Report Series No 810. World Health Organization, Geneva 1991, 103 pages, Sw.fr. 14, US$12.60, developing countries Sw.fr. 9.80

Essential Elements of Obstetric Care at First Referral Level World Health Organization, Geneva, 1991, 72 pages Sw.fr. 14, US$12.60, developing countries Sw.fr. 9.80

Surgical Obstetrics edited by Warren C. Plauche, John C. Morrison & Mary Jo O'Sullivan. W. B. Saunders Company, Philadelphia, London, 1992, 512 pages, fully illustrated, £52.00



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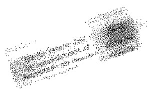

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Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London

Volume 99, Number 5, May 1992 BJOGAS 99(5) 355–444 1992 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

Edited by David B. Paintin

SUPER ARDUA

Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications

6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

50 YEARS EXPERIENCE

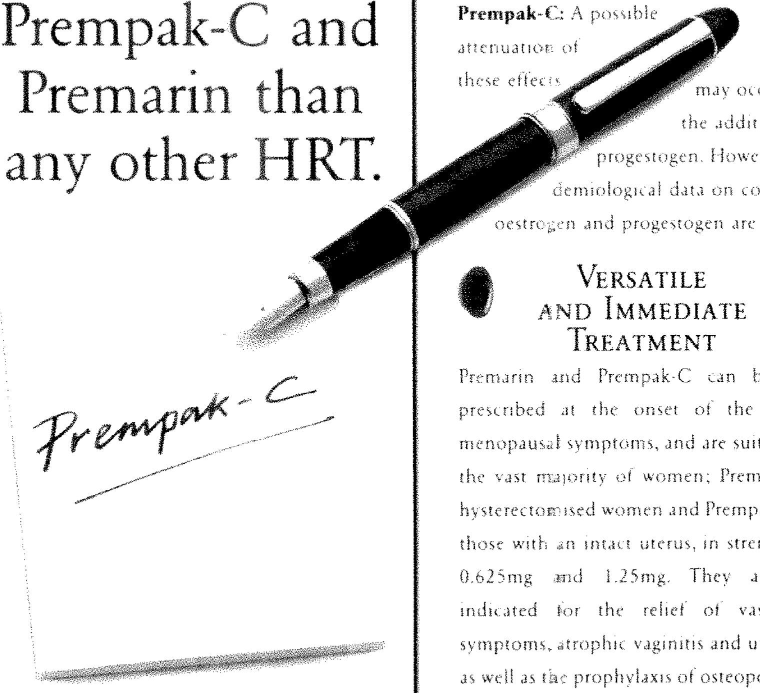
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



REDUCING CARDIOVASCULAR DISEASE RISKS

Premarin: A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users. The most common form of oestrogen used in all these studies was conjugated oestrogen, i.e. Premarin.

Prempak-C: A possible attenuation of these effects may occur with the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited.

VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women; Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625mg and 1.25mg. They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk.

COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1.65 and Prempak-C costs £3.98, for 28 days of therapy.[7]

PREMPAK-C

PREMARIN

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.

DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily. Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential.

CONTRA-INDICATIONS: Known or suspected pregnancy and during lactation. History of known or suspected cancer of the breast. Oestrogen dependent neoplasia. Undiagnosed abnormal genital bleeding. Active thrombophlebitis or thromboembolic disorders. Acute or chronic liver disease. Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease.

WARNINGS AND PRECAUTIONS: Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship. It is not known whether concurrent progestogen influences this risk. The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma. Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction. Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop. Certain endocrine and liver function tests may be affected. Rarely idiosyncratic hypertension may occur. Discontinue treatment prior to surgery or prolonged immobilisation. Gallbladder disease. Insulin requirements may be altered. Premarin is not an oral contraceptive.

SIDE EFFECTS: The following have been reported with oestrogen therapy: premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps.

PRODUCT LICENCE NUMBERS: Premarin 0.625mg PL0011/0165 Premarin 1.25mg PL0011/0166 Premarin 2.5mg PL0011/0167 **BASIC NHS PRICE:** Premarin 0.625mg £1.65 (28 days). For full prescribing information please refer to data sheet.

PREMPAK-C **USES:** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.

DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily and one norgestrel 0.15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy.

CONTRA-INDICATIONS: As for Premarin.

WARNINGS AND PRECAUTIONS: As for Premarin. Prempak-C is not an oral contraceptive.

SIDE EFFECTS: As for Premarin. Breakthrough bleeding and spotting. Change in menstrual flow, dysmenorrhoea, amenorrhoea.

PRODUCT LICENCE NUMBERS: Prempak-C 0.625mg PL0011/0161 Prempak-C 1.25mg PL0011/0162.

BASIC NHS PRICE: £3.98 - 28 days. For full prescribing information please refer to data sheet.

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PREMARIN*
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

PREMPAK-C*
(Conjugated Oestrogens + Norgestrel)

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Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493

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British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 355–359

COMMENTARIES

Eclampsia in the United Kingdom. The 'BEST' way forward

During 1992 a survey of all the cases of eclampsia in the United Kingdom is being carried out by the British Eclampsia Survey Team (BEST) under the auspices of the Medical Audit Unit of the Royal College of Obstetricians and Gynaecologists. The survey is the first truly national survey of eclampsia in over half a century. It is supported by the Royal College of Obstetricians and Gynaecologists, the Royal College of Midwives, the Royal College of General Practitioners and by the General Medical Service Council of the British Medical Association. Why is such a survey necessary; what will be learned; and what developments can be expected from the enquiry?

Eclampsia remains a significant problem worldwide. In the Western world eclampsia remains one of the major causes of maternal mortality (Department of Health *et al.* 1991; Hibbard 1973). In developing countries (which have maternal mortality rates 100–200 times higher than Europe and North America) it is estimated that 10% of all maternal deaths are associated with eclampsia and there is no evidence that the risk of dying from hypertensive disorders of pregnancy is decreasing in either Africa or Latin America (Duley 1992).

The first and only national review of eclampsia in the United Kingdom was made by Eden (1922). He reviewed the Registrar Generals' Report on eclampsia in England, Scotland, Wales and Northern Ireland and estimated an incidence of 4% in hospital labours and a case fatality of 22%. Eden included hospital births only, which biased his figures as women labouring in hospital at that time were a select group, unlikely to be representative of the maternity population as a whole. Nevertheless Eden's is the only attempt to gain a comprehensive overview of eclampsia in the United Kingdom.

There has been remarkably little progress in our understanding of eclampsia in this country in the 70 years since Eden's review in 1922, we do not know the incidence of eclampsia in the UK today, nor the maternal or fetal case fatality rates, nor the extent of morbidity associated with the condition. We do not know if there are geographic variations in the incidence of eclampsia and have limited information about which forms of treatment are used.

Over the last 30 years there have been several studies of eclampsia in various parts of the UK. McClure Browne (1961) reported the incidence of eclamptic convulsions as 0·15% in primigravid pregnancies in a hospital-based population. In two more recent population-based studies the incidence of eclampsia was half that found by McClure Browne; 0·074% in the Grampian region of Scotland between 1965–77 (Templeton 1977) and 0·072% in the Cardiff Birth Survey data between 1965–74 (Wightman 1978). The incidence was lower still (0·036%) in all women delivered in hospital in Oxford between 1978–86 (Redman 1988).

These figures suggest that the incidence of eclampsia in the United Kingdom has decreased since 1965. It is not possible to be categorical about the decrease because both McClure Browne's and Redman's estimates are limited as they are derived from hospital data and may not reflect the experience of the population as a whole, and McClure Browne included only primigravid women (who are high risk group for developing eclampsia). In the United Kingdom there are *no* systematically collected population-based data which allow us to assess with confidence if either the incidence of eclampsia or the rates of morbidity or mortality associated with it have changed over time.

The most reliable population-based data come from New Zealand, where eclampsia is statutorily notifiable. These demonstrate a real fall in the incidence from 0·32% of all births in 1928–33 to 0·06% in 1959–61. Over the same period the case fatality rate fell from 18·9% to 0·8% (Medical Research Council of New Zealand 1962). In Sweden the incidence of eclampsia declined from 0·11% in 1951–55 to 0·022% in 1971–80. The case fatality rate decreased dramatically from 13·9% in 1951–55 to 2·4% in 1956–60 but remained static thereafter (Hogber 1985). In the USA, a recent epidemiological study found a diagnosis of eclampsia in 0·056% of discharge summaries of women who gave birth to live-born or stillborn babies in hospital during 1979–86 (Saftlas 1990).

These studies from New Zealand, Europe and North America do indicate a reduction in the incidence of eclampsia in developed countries over the last 50 years, to levels that are somewhere around 1 per 2000 deliveries. However, there is still no room for complacency. Hypertensive disorders of pregnancy (eclampsia and pre-eclampsia) have been one of the three major causes of maternal mortality in England and Wales for the last 24 years and the major cause for the last 9 years (Department of Health *et al.* 1991). Moreover, in the United Kingdom between 1985 and 1987, over three quarters (81%) of maternal deaths from hypertensive complications of pregnancy were judged to reflect substandard care, and most of these (70%) involved specialist services in hospitals rather than the patients themselves or community services (Department of Health *et al* 1991). Do these figures indicate that substandard care is a generalized feature of most cases of eclampsia or, as is more likely, that this is an atypical subset? The profession needs to know so that a concerted effort can be organized to avoid these tragedies.

The problem is not limited to that of maternal mortality. Severe morbidity associated with eclampsia includes cerebral haemorrhages, cortical blindness, renal failure, disseminated intravascular coagulopathy, pulmonary oedema and psychosis (Villar 1988). In Sweden during 1976–80 nearly 15% of affected women had serious maternal complications in addition to eclamptic convulsions (Moller 1986), but the magnitude of this problem in the United Kingdom is completely unknown—it has never been measured. There are also perinatal problems. Infants born to eclamptic women are commonly growth retarded, born preterm or both and these problems carry their own well-known burdens of morbidity and mortality (Wightman 1978). Once again, we do not know the extent of this burden in the United Kingdom nor do we know how often eclampsia is associated with the death of well grown and mature fetuses.

With an estimated incidence of 1 in 2000 deliveries, eclampsia is rare and will be encountered by the busiest UK specialist only about once every 2 years—too infrequently to allow the development of the skills or insights that come with frequent experience. To make progress in the management of this condition not only do we need to know the true scale of the problem and its sequelae but also to aggregate the scattered experiences of specialists around the country to create a corporate body of information, available to all. This will be a prime objective of BEST.

During 1992, notifications of cases of eclampsia are being sought from all 17 National Health Service Regions, from over 275 hospitals and senior midwives and from all obstetric consultants (there are over 1000) in the UK. BEST estimates there will be 350–400 cases, so that, on average, clinicians will be either not involved at all, or asked to report just one or two cases.

Under conditions of the strictest confidentiality, information about each woman with eclampsia is being collected in a retrospective case-note review by a medical practitioner. Social and demographic data and data on maternal health, antenatal care, features of eclampsia, methods of management and maternal and perinatal outcomes are being included. Each woman's general practitioner is also being asked to complete a separate questionnaire in an effort to collect more information about her antenatal care and about minor post-eclampsia morbidity, both of which are often inadequately recorded in hospital case-notes.

Combining and recording the national experience of eclampsia will provide answers to some crucial questions. For example eclampsia, like pre-eclampsia, is heterogeneous and the single label of eclampsia covers a multiplicity of presentations, not all of them likely to be equally dangerous. What distinguishes a mild from a severe case? Do the mild cases occur mainly after delivery or at full term? How common are severe cases and how do they present? Are there any commonly used indices which can distinguish a severe from a mild case? Measuring the relative frequency and dangers of the major variants of eclampsia will provide clinicians with information which is of practical value on the rare occasions that they are required to care for women with eclampsia.

It is possible that the BEST survey will reveal obvious gaps in methods of management which can be closed with immediate and important benefits for all. However, surveys of this type have limitations: they can demonstrate association but not cause and effect. It will not be possible to conclude that one method of management is definitely superior to another; but the BEST survey will construct an essential foundation of knowledge upon which multi-centre controlled trials can be planned and implemented.

Medical audit is an active purposeful process in which goals are set and progress in reaching those goals are regularly reviewed. A prime aim of BEST is to establish a continuing British Eclampsia Register which would audit the condition in the United Kingdom and help to ensure that future progress is made. The Register would ideally be run under the aegis of the Royal College of Obstetricians and Gynaecologists Medical Audit Unit, would be organized on a regional basis and would collect only very limited information on women with eclampsia from 1993 onwards. Explicit targets should be set. In our view the profession should aim to halve the national incidence of eclampsia every 5 years, starting in 1994. Once the audit processes are in place to provide the necessary feedback, there is every reason to believe that this goal could be achieved.

In 1922 after completing the first national review of eclampsia Eden stated 'collective work planned and tested by critical minds is the path along which progress will probably come in the future' (Eden 1922). He hoped that his example would be widely followed; but it was not and knowledge about the pattern of eclampsia in the UK has declined rather than advanced, despite appeals by Davies for 'future national studies based on populations' (Davies 1971) and from one of us calling for 'regular reviews of all cases of eclampsia' (Redman 1988). Seventy years after Eden's paper it is time to heed his advice and in addition to make a co-ordinated attempt to begin to eliminate eclampsia in this country. A first and simple step that all obstetricians can take is to support the newly established British Eclampsia Survey Team.

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British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 357–358

Terminology used in early pregnancy loss

The use of the term 'abortion' to describe an unwanted early pregnancy loss is frequently reported as hurtful to women (Chalmers & Hofmeyr 1989; Oakley *et al.* 1984). Overtones of 'induced' or 'illegal' abortion often contrast with women's disappointment at the time of the unwanted loss. Some years ago Beard *et al.* (1985) appealed for attention to be directed to the psychological meaning of the term 'abortion' for women who experience a pregnancy loss unwantedly.

It appears that publications in the *British Journal of Obstetrics and Gynaecology* have taken heed of this appeal. A count of the titles of papers published in this Journal referring to unwanted early pregnancy loss in 1981–2 and 1989–90 revealed a change in terminology used before and after the editorial by Beard *et al.* (1985) (Table 1). Whereas almost all the papers at the start of the decade used the term 'abortion' in their titles, none of those published later did so.

Little research has, however, systematically examined the meaning of terminology regarding pregnancy loss for women. Some exploratory research in this area suggests that the preferred terminology, at least from the woman's perspective, may be culturally determined.

Cross cultural research into womens' preferences for the use of 'abortion' or 'miscarriage' indicates that women from different cultural backgrounds may not be equally concerned about medical terminology with its possible negative emotional overtones. In a study of 106 women experiencing a first pregnancy loss before 28 weeks, 32 expressed a dislike for the word 'abortion', 37 were indifferent to its use whereas 25 preferred it. In this small pilot sample, women of mixed cultural origin disliked the term more than others; White and Indian women were predominantly indifferent to its use and African women expressed a liking for it (Chalmers & Meyer 1991). It is apparent that cultural variations in the meaning of medical terminology may occur and must be recognized by doctors. Further research is needed to explore this issue.

Research and comment has concentrated on the use or misuse of the term 'abortion' for describing spontaneous early pregnancy loss. There are, however, other phrases used when caring for women who lose babies which may also have emotionally negative connotations and which should be examined.

Terms such as 'failed pregnancy', 'incompetent cervix', 'inadequate germ plasma', and 'abnormal chromosomal material' are often used by professionals. Whereas these may have objective medical meanings for the doctor their meaning to the woman may be different. Women may focus on the words 'failed', 'incompetent'. 'inadequate' and 'abnormal', all of which are part of everyday English, and apply them, not to their physiological functioning but to themselves, as persons. Feelings of failure, shame, guilt, insecurity and depression are recognized reactions to an unwanted miscarriage (Graves 1987; Leroy 1988; Oakley *et al.* 1984; Pizer & Palinksi 1986). The use of medical terminology which carries negative connotations for the lay person may contribute to the development of negative self perceptions, particularly in those already predisposed to think ill of their miscarriage experience.

Table 1. Terminology used in titles of papers relating to miscarriage in the *British Journal of Obstetrics and Gynaecology*

Terminology	No. of articles 1981–82	1989–90
Abortion	7	0
Cervical incompetence	1	0
Preterm delivery	0	1
Early pregnancy failure	0	1
Miscarriage	0	6

Womens' difficulty in adjusting to a miscarriage (Chalmers & Hofmeyr 1989; Oakley *et al.* 1984) may be compounded by the procedure followed with regard to the lost baby. The medical and nursing professions commonly refer to the 'products of conception'. Women, in contrast, tend to think of their loss as a 'baby'. In addition, the outcome of the pregnancy is not usually buried: it is 'disposed of', either by sluicing or incineration. Contradictions such as these emphasize a discrepancy between some womens' views of their pregnancy loss and those of their attending professionals: for the women the pregnancy is real and their wishes may be for a burial of the lost baby, whereas for the medical profession the conceptus does not yet warrant such 'human' recognition.

It is possible that recent developments in technology may have exacerbated the difficulty of adjusting to an early pregnancy loss. In some traditional societies (Larsen *et al.* 1983) women do not acknowledge conception until 4–6 months into pregnancy. In more modern societies women are aware of their pregnancies far earlier: a mean gestational age of 2·1 months has been reported in some groups of western women (Chalmers 1990). This trend towards earlier acknowledgment of conception follows the encouragement of women to seek antenatal care earlier. In addition, the application of technologies, such as sonography, allows early diagnosis of conception. The psychological consequencies of these medical developments may well be an earlier identification with the 'baby' by the parents, facilitated by visual and auditory images of the unborn baby. The unwanted loss of this baby could result in disappointment even if it occurs early in the pregnancy.

Many women report not having recovered emotionally from their miscarriage experience months after the event (Chalmers & Meyer 1991). The absence of clear 'rites of passage' may contribute to this inability to adjust. The lack of recognition of the loss as a baby, particularly if the miscarriage takes place in very early pregnancy; the absence of any burial ceremony to mark the recognition of lost life; the inability to identify a place of remembrance such as a burial site; the lack of social recognition of the woman as a mother even if only of a baby that has died and the expectation that mourning is not needed or is inappropriate in the event of early pregnancy loss, may make mourning more difficult.

Recent recommendations regarding the management of a stillbirth recognize the importance of having something to remember about the baby to facilitate mourning and acceptance of the experience (Barr 1986; Bourne & Lewis 1991). Simply seeing and holding the baby at birth helps: this is further aided by having a photograph or a sonograph for remembrance. It may be that some of these ideas are applicable to earlier pregnancy loss as well particularly when this loss is viewed as stressful by the woman. Some research indicates that seeing the outcome of a miscarriage before 28 weeks, if this resembles a fetus and not a mass of tissue, is regarded positively by the woman (Chalmers & Meyer 1991). Further research is needed to assess whether this finding can be confirmed, particularly among women of differing cultures.

Variations in cross cultural perceptions, as well as individual differences in the meaning of a miscarriage experience, must always be acknowledged, explored and understood when caring for the individual woman. Moreover, changes in practice including those of language and behaviour are worthy of consideration in the process of providing medical and emotional care for women who miscarry.

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British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 358–359

Action in international medicine and maternal health care in developing countries

Action in International Medicine (AIM), formed in 1988, is an international organization whose members are some 88 institutes or academies of medicine and professional organizations based in 28 countries. AIM intends to work alongside international agencies and governments to assist in the provision of health care in developing countries. It will be capable of providing direct support for the professionals of its own member bodies and in addition will be free to assist those working for non-governmental organizations.

The Royal College of Obstetricians and Gynaecologists (RCOG) was among the first of AIM's members and was represented at AIM's first World Assembly in Toronto in August, 1991. A report of the Assembly, together with an account of some projects which AIM has already supported has been published recently (Haines 1991). The purpose of the Assembly was to reach agreement on the focus, objectives and resources of the organization. Some of the Assembly's conclusions had direct relevance to the provision of maternity care. The first of these was AIM's conviction that the development of district health systems is the key to the improvement of health in many developing countries. It is perceived that there is a crucial deficiency at this point in many health services. Since the Alma Ata Declaration in 1978, primary health care has received much attention and has developed well in many countries. At the same time tertiary care has been the beneficiary of considerable resources. In many countries the result is that while sophisticated obstetric treatment may be available in the main centres, women in deprived and especially rural areas do not have access to basic but life-saving interventions such as caesarean section or operative vaginal delivery. Maternal mortality, the natural outcome of such service deficiencies, now shows the greatest differential of all public health indicators between the developed and the developing nations. It is not surprising therefore that the Assembly in Toronto also identified the Safe Motherhood Initiative as an issue with which AIM should concern itself. The aims of the Initiative backed by the major international development and health agencies have been described. Belsey (1990) reported that the 'middle level' of maternity care is contracting both in quality and quantity in the rural areas of many countries and he stressed the importance of promoting community-based maternity care and of providing skilled obstetric care at the first level of referral.

AIM's World Assembly ended in a decision to issue the Toronto Declaration on Global Health Care, in which delegates and representatives committed themselves to the promotion of a culturally appropriate infra-structure of health care worldwide, such that preventative, curative and rehabilitative services are effectively integrated at the district level. The declaration also calls on professional organizations to encourage their members to seek ways of improving the education and training of all health professionals working with deprived populations, and calls on individuals to use every means at their disposal to bring about the provision of health care where it is absent and its improvement when it is inadequate.

AIM's conclusions are of course based on numerous arguments over recent years. For example Brown (1979) pointed out how the way in which medical education has been exported from industrial to developing countries has been inappropriate and not conducive to improving the health of the population as a whole. In the same year, Mburu (1979) described how in Kenya, a representative developing country, the rhetoric in health planning is not consistent with actual health programmes. He listed some of the reasons why the distribution of physicians and other health workers continued to be inequitable.

AIM then is presenting serious challenges to its member organizations, and the RCOG with its large international membership must surely respond. As a body the RCOG is heavily involved in the postgraduate medical education of doctors from developing countries. Is it time perhaps to look at the membership examination and question whether it should include some elements concerning the causes of maternal mortality on a global scale, or about health care provision? The double sponsorship scheme does now incorporate an annual educational meeting but could more be done to make the scheme more appropriate? Are the sponsored trainees required to assess likely cost benefits of the new methods and skills they learn if applied in their home environment? What can we do to ensure that their training here is not deleterious by diverting their attention from the real needs of their own countries? On the credit side the College has made a decision to develop a Diploma Course in Maternal and Neonatal Health together with the Liverpool School of Tropical Medicine and Hygiene although, to date, no one has been found who is prepared to fund it. The course, if successfully initiated, should provide training in appropriate skills for those most interested in the provision of maternity care. Courses in epidemiology, community health, medical manpower, plus management and educational skills should equip its diplomats to become leaders in the field of maternity care provision.

As individuals, fellows and members working overseas are in the strongest position to contribute. This could include taking steps to improve the obstetric training provided for those young doctors about to become district doctors. In many countries these non-specialists have to undertake quite complicated emergency obstetrics, and indeed obstetrics and gynaecology together provide the great majority of the surgery they have to undertake. Overseas fellows and members ought also to note that AIM intends to support the establishment and spread of sustainable models of district care. New initiatives being set up by themselves could receive support from AIM in the form of specific training in management or clinical skills. AIM also intends to link health professionals with their counterparts in other countries where it is judged that one can benefit from the others' experience. Professional organizations in overseas countries could also play an important role by lobbying their governments to increase the pay, status and conditions of doctors working at district level. AIM sees this as a very necessary step in developing and keeping a skilled workforce at district level.

For those individuals who would wish to be more closely linked with AIM and receive its newsletter, individual membership is available at the cost of £15 per year and can be arranged by contacting the AIM Office (Action in International Medicine, Windeyer Building, 46 Cleveland Street, London W1P 6DB). In addition, to enable it to respond to requests for help with projects AIM intends to develop an international register of health professionals with appropriate skills and experience in collaboration with the International Health Exchange (formerly Bureau of Overseas Medical Service). Fellows and members both overseas and in the United Kingdom who feel they could help should register.

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British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 360–363

A randomized prospective study comparing delivery with metal and silicone rubber vacuum extractor cups

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ABSTRACT

Objective To determine the relative benefits and complications of assisted vaginal delivery with metal and silicone rubber vacuum extractor cups.
Design Prospective randomized controlled study.
Setting A busy referral maternity hospital in Kathmandu, Nepal.
Subjects 101 women were assigned to delivery with the Silc-cup and 98 to delivery with the metal cup.
Main outcome measures Success rate at achieving delivery with the assigned instrument and incidence of neonatal trauma. Analysis was by 'intention to deliver' with women remaining in their original group regardless of the eventual mode of delivery.
Results Randomization resulted in two groups of women similar in respect of age, parity, gestation and indication for delivery. The overall success rate was similar for the two instruments (Silc-cup 85% and metal cup 87%). The Silc-cup was more likely to fail if there was excessive caput (seven failures compared with one in the metal cup group). The frequency of clinically significant maternal trauma was low in both groups. There were fewer babies with clinically significant scalp trauma in the Silc-cup group (22%), compared with the metal cup group (37%).
Conclusions The data indicate a greater tendency for the Silc-cup to fail when excessive caput is present but that metal cups are associated with increased scalp injuries.

The vacuum extractor is widely used in developing countries as the instrument of first choice for operative vaginal delivery. It is chosen because it is less traumatic than forceps to the mother, particularly in circumstances where the maternal pelvis is relatively smaller than in developed countries.

There has been concern, however, that the metal cup may be associated with neonatal trauma (Ahuja *et al.* 1969; Augero & Alvarez 1962) and recent research has concentrated on developing a cup that would minimize scalp injuries. Early reports suggested that this could be achieved with the new silicone rubber cups (Berkus *et al.* 1980; Dell *et al.* 1985).

A number of different soft cups have been introduced. Four randomized controlled trials comparing the soft with the metal cups have been reported. Hammarstrom *et al.* (1986) compared the Kobayashi and Malmström cups. Cohn *et al.* (1989) and Kuit *et al.* (1990) compared the Silc and Bird (metal) cups. Hofmeyr *et al.* (1990) looked at Silc/silicone versus Bird/O'Neil. The results of the first three studies are the subject of a meta-analysis in the Oxford Database of Perinatal Trials (Johanson 1991a). The pooled data analysis showed that soft cups were significantly more likely to fail to achieve a vaginal delivery. There was no difference between the two groups in terms of maternal injury but there was a trend towards more significant scalp injuries and phototherapy requirements in the metal cup group.

No previous randomized assessment of assisted delivery has been reported from a developing country. It is important that studies of different instruments be undertaken in different situations to determine the best instruments for local use.

Subjects and methods

The Kathmandu Maternity Hospital is the principal referral centre, both for maternity and gynaecological problems, in Nepal. Around 12 000 babies are born there per year. The vacuum extractor is used for 4% of deliveries, the caesarean section rate is 5% and forceps are used in 1%.

Women eligible for entry into the study were all those with a singleton pregnancy of more than 37 weeks gestation with a cephalic presentation and where instrumental delivery was required.

Once a decision had been made that the pregnancy was suitable to be included in the trial, full details of the vaginal examination findings were recorded and randomization was undertaken by sealed envelope.

The metal cup used in Kathmandu is the original Malmström cup (5 cm metal cup with central chain and suction pipe). The soft-cup was the 6 cm 'Silc-cup' (Menox-AB,

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Table 1. Characteristics of the two study groups

Variable	Silc-cup group (n=101)	Metal cup group (n=98)
Age (years)	23 (4)	23 (4)
Gestational age (weeks)	39·8 (1 4)	39·7 (1·4)
Birthweight (kg)	2·8 (0·5)	2·9 (0·5)
Nulliparity	80 (80%)	76 (76%)
Meconium stained amniotic fluid	36 (36%)	41 (41%)
Indication for assisted delivery		
Delay in second stage	45 (44%)	45 (46%)
Fetal distress	22 (22%)	19 (19%)
Delay and distress	19 (19%)	19 (19%)
Shorten second stage	15 (15%)	15 (15%)
Position of head		
Occipito-anterior	77 (76%)	71 (72%)
Occipito-transverse/posterior	19 (19%)	22 (23%)
Unknown	5 (5%)	5 (5%)

Results are mean (SD) or n (%) values as appropriate.

Sweden). The cups were attached to a hand-pump and the pressure was taken directly to 0·6–0·8 kg/cm^2. The first pull was with the next contraction. The time limit of application was 15 min and the limit of re-applications was two.

The maternal assessment was performed by the obstetrician performing the delivery and the paediatric assessment at 24–48 h by the hospital paediatrician. All mothers and babies were reviewed prior to discharge by R.C.

With 200 subjects the trial would have a power of 70% (at P=0·05) to detect a 50% decrease in the incidence of scalp trauma (from 20% to 10%) or a 50% increase in failure rate (from 10% to 20%).

The comparison was of 'an intention to deliver', the women remained in the originally allocated group regardless of the final mode of delivery. Frequency data were analyzed using the χ^2 test and results are presented as odds ratios and 95% CI.

The study was approved by the hospital ethics committee. Consent was obtained prior to randomization.

Table 2. Details of delivery in the two groups

	Silc-cup group (n=101) n (%)	Metal cup group (n=98) n (%)
Actual mode of delivery		
Metal cup	3 (3)	85 (87)
Silc-cup	86 (85)	2 (2)
Forceps	6 (6)	3 (3)
Caesarean section	2 (2)	1 (1)
Spontaneous vaginal	4 (4)	7 (7)
Operator status		
SHO	76 (75)	74 (76)
Registrar	24 (24)	21 (21)
Consultant	1 (1)	3 (3)
Reasons for failure		
Excess caput	7 (7)	1 (1)
Instrument not ready	1 (1)	4 (4)
Leaking apparatus	0 (0)	6 (6)
Failure of descent	4 (4)	2 (2)
Cord prolapse	2 (2)	0 (0)

Table 3. Maternal injury in the two study groups

	Silc-cup group (n=101) n (%)	Metal cup group (n=98) n (%)
Perineal tears		
None	6 (6)	8 (8)
1st degree	1 (1)	4 (4)
2nd degree	93 (92)	84 (84)
3rd degree	1 (1)	2 (2)
Vaginal tears		
None	97 (96)	92 (94)
Midvaginal	2 (2)	3 (3)
Forniceal	2 (2)	3 (3)
Cervical tears	3 (3)	1 (1)
Extension of episiotomy	14 (14)	22 (22)
Vulval haematoma	1 (1)	1 (1)

By the end of the study 199 women had been recruited. None was excluded from analysis.

Results

Of the 199 pregnant women in the trial, 101 were assigned to delivery by the Silc-cup and 98 to delivery by the metal cup. The comparability of the two groups is presented in Table 1. There were no significant differences between the two groups in maternal or fetal variables or in terms of the attitude or station of the head and in terms of the amount of caput in the two groups. There were more deliveries undertaken before full dilatation in the metal-cup group (n=4) than in the Silc-cup group (n=1).

The details of the deliveries are shown in Table 2. There were no significant differences between the two types of cup, in both groups the majority of deliveries were undertaken by senior house officers.

The reasons for failure are given in Table 2. The metal-cup was not used on four occasions because it was not ready and on six occasions there was leakage. There were two failures in the Silc-cup group due to cord prolapse, the cup being too large to apply without catching the cord. The Silc-cup was also more likely to fail if there was excess caput. If one looks only at the group of babies in the study with ++ or more of caput (20 in the Silc-cup group compared with 28 in the metal group) the

Table 4. Neonatal morbidity in the two study groups

	Silc-cup group (n=101)	Metal cup group (n=98)
Significant scalp injury		
Scalp lacerations	1 (1)	3 (3)
Moderate bruising	21 (21)	33 (33)
Severe bruising	0 (0)	1 (1)
Total	22 (22)*	37 (37)
Phototherapy	9 (9)	12 (12)
Feeding problems	3 (3)	2 (2)
Activity reduced	7 (7)	2 (2)
5-min Apgar score <7	9 (9)	17 (17)

*Odds ratio 0·46 (95% CI 0·24–0·86), P<0·05.

Table 5. Effect of soft *versus* hard vacuum extractor cups on failure to deliver with selected instrument

Study	Soft cup *n*	(%)	Metal cup *n*	(%)	Odds ratio (95% CI)
Hofmeyr *et al.* (1990)	3/13	(23)	0/18	(—)	12·8 (1·2–99)
Cohn *et al.* (1989)	21/131	(16)	13/127	(10)	1·7 (0·8–3·4)
Hammarstrom *et al.* (1986)	9/50	(18)	1/50	(2)	5·8 (1·6–21)
Kuit *et al.* (1990)	5/50	(10)	2/50	(4)	2·7 (0·5–14)
Present study	15/101	(15)	13/98	(13)	1·14 (0·5–2·54)
Typical odds ratio (95% CI)					1·75 (1·55–2)

increased risk of failure was highly significant [7 of 20 (35%) *vs* 1 of 28 (4%); odds ratio 14 (95% CI 1·6 to 130)].

There were no significant differences between the two instruments in terms of maternal morbidity (Table 3). There were no differences between the two groups in terms of anaesthesia for delivery; 88% in the metal group and 92% in the Silic group had perineal infiltration alone. Five women in the metal group had a blood loss of >500 ml compared with two in the Silc group. There were no significant differences between the two groups in terms of severity of perineal bruising or post-delivery analgesic usage. Eight women in the Silc group had urinary discomfort post-delivery compared with only one in the metal group (odds ratio 8·3, 95% CI 1·02–68).

Neonatal morbidity is detailed in Table 4. There were significantly more babies in the metal cup group who had moderate or severe scalp injuries. Although there were more babies born by the metal-cup who required phototherapy for jaundice and more babies who had low 5-min Apgar scores (<7) neither of these differences was statistically significant. The differences in activity and feeding were not statistically significant. There were no intrapartum or neonatal deaths and there were no babies who developed convulsions. There were three babies with major congenital abnormalities, two with meningomyelocoeles and one with an omphalocoele.

Discussion

This study confirms a number of previous findings with regard to the differences between the soft and metal cups, the two most important being the increased failure rate of the Silc-cup (particularly if excess caput is present) and the second being the finding that the metal cup is significantly more likely to injure the baby's head. The typical odds ratios for all currently available data for these two outcome variables are shown in Tables 5 and 6.

There is good evidence that the ventouse should be used as the instrument of first choice for operative vaginal delivery, primarily because it is less likely to be associated with severe maternal injuries (Johanson 1991b). It is still unclear as to whether forceps or ventouse are more likely to significantly injure the baby. It would appear that when using the ventouse scalp injuries are less common if soft-cups are the preferred instruments.

It is also important to reduce the number of occasions on which the chosen instrument fails. The metal cup that was used in Kathmandu was of the original Malmström design which required assembly immediately before usage. This was time-consuming and resulted in the instrument not being ready on four occasions. The rubber tubing was not new and this contributed to the leakage which resulted in failure on six occasions. In this study the metal cup was only associated with three true failures (success rate of 97%). It is likely that if the newer Bird-metal cups (including the 6 cm size) had been used (with new tubing) the equipment problem failures would not have occurred.

Although less traumatic to the baby the Silc-cup resulted in an increased frequency of postdelivery urinary discomfort. This surprising finding may have been due to the fact that sometimes as the head approaches the introitus the edge of the soft cup lifts up catching the maternal tissues under it as the cup reapplies. The finding that three women in the Silc-cup group had cervical lacerations compared with only one in the metal group was not statistically significant. Nevertheless, this injury raises questions about whether the delivery was undertaken before full dilatation or whether sufficient attention was given to ensuring that no cervical tissue was caught under the cervix. It is possible that the Silc-cup is more likely to cause this problem being of a slightly larger diameter. The most recent maternal mortality report (Department of Health *et al.* 1991) contained two deaths that implicated similar misuse of the ventouse.

We conclude that the Silc-cup is an important new instrument which was used successfully with minimal maternal or neonatal trauma. However, care should be taken not to use it in situations where it is likely to fail (particularly where there is excess caput) and additional care should be taken to ensure that

Table 6. Effect of soft *versus* hard vacuum extractor cups on significant scalp trauma

Study	Soft cup *n*	(%)	Metal cup *n*	(%)	Odds ratio (95% CI)
Cohn *et al* (1989)	18/131	(14%)	23/127	(18%)	0·7 (0·4–1·4)
Hammarstrom *et al.* (1986)	2/50	(4%)	6/50	(12%)	0·3 (0·1–1·4)
Kuit *et al.* (1990)	3/50	(6%)	11/50	(22%)	0·23 (0·06–0·87)
Present study	22/101	(22%)	37/98	(38%)	0·46 (0·24–0·86)
Typical odds ratio (95% CI)					0·5 (0·46–0·54)

the edges of the cup should not be allowed to catch either cervical or introital vaginal tissue.

Acknowledgments

We would like to thank Dr D. S. Malla, FRCOG, Director of the Maternity Hospital and other colleagues at the hospital for their co-operation in performing this study.

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Received 17 September 1991
Accepted 10 January 1992

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 364–367

OBSTETRICS

Intra-operative blood loss during elective lower segment caesarean section

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ABSTRACT

Objective To measure intra-operative blood loss at elective lower segment caesarean section and to compare estimated wtih measured blood loss.
Design Prospective observational study. Blood loss was measured in patients who underwent lower segment caesarean section in the course of routine hospital activity.
Setting Tsan Yuk Hospital (Hong Kong), which is affiliated to the University of Hong Kong, 1990–1991.
Subjects Forty women (mean age 29 years) with singleton pregnancies (mean gestation 38 weeks) delivered by elective lower segment caesarean section under general anaesthesia (mean birthweight 3177 g).
Main outcome measure Intra-operative blood loss measured by the alkaline haematin method (intra-assay co-efficient of variation 2·2%).
Results The mean measured blood loss was 487 ml (SE 40, range 164–1438). The mean estimated blood loss was 425 ml (SE 31) range 100–1300; mode 400). Observer error in estimating blood loss was higher if measured blood loss >600 ml. One patient received a blood transfusion and another had a post-operative haemoglobin level <10·0g/dl.
Conclusion Blood loss at elective lower segment caesarean section was usually <500 ml and was estimated with reasonable accuracy. However, there was a tendency to under-estimate blood loss when the measured loss exceeded 600 ml.

In recent texts estimates of blood loss during elective lower segment caesarean section range from 600 ml (Beazley 1989) to 1000 ml (Letsky 1987). Earlier reports have been based on small numbers and heterogeneous groups of patients (Dieckmann & Daily 1935; Dieckmann & Stout 1950; Tatum 1953; Wilcox *et al.* 1959; Pritchard *et al.* 1962; Brant 1966). The methods used to determine blood loss were crude and often imprecise. More recently, sophisticated methods have been used to measure changes in plasma volume (Ueland 1976) but such measurements only provide an indirect assessment of the volume of circulating blood actually lost. By contrast, the use of a Stomacher Lab Blender (Model 3500, Seward Laboratories, London, UK) and alkaline haematin method for measurement of blood loss provide results which are accurate and reproducible (Newton *et al.* 1977; Shaw 1977; Duthie *et al.* 1990). We measured the intra-operative blood loss during elective lower segment caesarean section, performed by junior obstetricians, under general anaesthesia.

Subjects and methods

Forty women (30 multiparae and 10 primiparae) were studied. All of them were delivered by elective lower segment caesarean section between 38 and 40 weeks gestation under general anaesthesia. None of the women had hypertension, diabetes, anaemia, sepsis or meconium stained amniotic fluid. The operations were performed by an obstetrician who had either passed the MRCOG examination within the previous year or who was about to take the MRCOG examination. The latter were supervised by an obstetrician with the MRCOG qualification.

Blood loss was measured using the alkaline haematin method (Newton *et al.* 1977; Shaw 1977; Duthie *et al.* 1990). One hour before the operation, 4 ml peripheral venous blood was collected from each woman for measurement of their haemoglobin level using the cyanmethaemoglobin method (Fairbanks 1976). During the operation the patient was draped with white linen and only white linen sanitary pads and gauze swabs were used. After the operation all the blood stained linen, sanitary pads, gauze swabs and blood clots were collected meticulously and placed in a cryovac plastic bag for blending. A 2 ml sample of the bloody fluid obtained by aspiration was collected for analysis and the total volume of bloody fluid aspirated was recorded.

The operations were all performed using standard surgical techniques and instruments. The abdomen was opened using either a midline subumbilical incision or a Pfannenstiel incision. The uterus was opened using a transverse lower segment incision, the baby was born, the umbilical cord was clamped

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and cut and the placenta was born by controlled cord traction. The edges of the uterine incision were held using 4 Green Armytage forceps. As soon as the baby was born the mother was given 10 U oxytocin or 0·5 mg ergometrine intravenously. The angles of the incision were secured and the lower uterine segment was repaired using gauge 1 chromic catgut. The vesico-uterine fold of peritoneum was repaired using 2/0 chromic catgut. The abdominal incision was closed in layers using standard techniques. The time interval between incision and closure of the skin was recorded by the nursing officer in charge of the operating theatre. After the skin wound was cleaned and dressed the vagina was cleaned and any blood obtained was added to the cryovac bag. At the end of the operation the volume of blood loss was estimated visually by inspecting the gauze swabs, linen, sanitary pads and drainage bottle. A consensus was reached between the surgeon and the anaesthetist and the estimated blood loss was recorded in the woman's case notes. The amniotic fluid was clear in all the women in the study.

General anaesthesia was used for all the operations. The following anaesthetic agents were used: thiopentone sodium, succinylcholine, atracurium, 1% enflurane, nitrous oxide and oxygen, pethidine, atropine and neostigmine. After administration of the oxytocin or ergometrine as a bolus, an intravenous oxytocin infusion was used in all cases. Forty units of oxytocin were added to 500 ml 5% dextrose and infused at the rate of 10 U/h.

The patients' blood pressure, pulse rate and SaO_2 were monitored throughout the operations. The haemoglobin concentration was measured in each case on the second morning after delivery.

A total of 2000 ml 5% (W/V) sodium hydroxide solution was added to each cryovac plastic bag containing blood stained linen, gauze swabs and sanitary pads. The bag was then placed in the Stomacher Lab Blender and processed at room temperature for 20 min (preparation A). Simultanenously, 100 ml 5% sodium hydroxide was added to a sample of 1 ml peripheral venous blood collected from the same patient (preparation B). After processing, a sample of the final mixture from each of the two preparations (A and B) was filtered and the absorbence of the clear supernatant was determined by spectrophotometry. Deviation of the absorbance at 550 nm with reference to the blank (A_{550}) was calculated. The volume of blood in the plastic bags, which represented the total amount of blood present in the stained linen and pads, was calculated from the following equation (Newton *et al.* 1977):

$$\text{Blood volume} = \frac{A_{550}\text{ of eluate (preparation A)} \times 2000}{A_{550}\text{ of venous blood (preparation B)} \times 100}$$

Also, 100 ml 5% sodium hydroxide was added to 1 ml of the aspirated fluid (preparation C). After processing, a sample of the mixture was filtered and the absorbance at 550 mm of the clear supernatant was measured. The volume of blood in the aspirate was obtained by the equation:

$$\text{Blood volume} = \frac{A_{550}\text{ of eluate (preparation C)} \times \text{Volume of aspirate}}{A_{550}\text{ of eluate (preparation B)}}$$

The total measured blood loss was obtained by adding together the volume of blood in each cryovac bag and the volume of aspirated blood. The intra-assay coefficient of variation for the measurement of blood volume by the alkaline-haematin method was 2·2%.

Results

The mean age of the 40 patients was 29 years (SD 4·1, range 19–38), mean length of gestation at delivery was 38 weeks (SD 0·5) and the mean birthweight was 3177 g (SD 475, range 2400–4550). The mean duration of the operation was 50 min (SD 15). In 23 women (58%) the indication for caesarean section was a previous lower segment caesarean section and evidence of cephalo-pelvic disproportion, in 15 (38%) the indication was breech presentation with another complication (intrauterine growth retardation, prolonged pregnancy or unfavourable pelvis) and in 2 (5%) the indication was type 2 placenta praevia (posterior).

The operation was performed through a transverse suprapubic incision in 19 women (47·5%), through a repeat transverse suprapubic incision in 7 (17·5%), through a midline incision in 9 (22·5%) and through a repeat midline incision in 5 (12·5%).

After the birth of the infant, 10 women received a bolus dose of 0·5 mg of ergometrine and 30 a bolus dose of 10 U of oxytocin. All the infants were born in good condition and the amniotic fluid was clear in all cases.

The mean measured blood loss was 487 ml (SE 40; range 164–1438). The mean estimated blood loss was 425 ml (SE 31; range 100–1300; mode 400). The relation between estimated blood loss and measured blood loss is shown in Fig. 1. The women were stratified into five groups based on the difference between measured and estimated blood loss and the average blood loss in each group was calculated. Fig. 2 shows the five groups, their average blood loss and the number of women in each group. The difference between measured and estimated blood loss related to the measured blood loss is shown in Fig. 3.

The mean pre-operative haemoglobin level was 12·1 g/dl (SE 0·21) and the mean postoperative haemoglobin level was 11·9 g/dl (SE 0·12). One woman, who had an estimated blood loss of 1300 ml (measured loss 1054 ml), received a blood transfusion immediately after the operation. Only one woman had a postoperative haemoglobin level <10·0 g/dl; she had an estimated blood loss of 600 ml and a measured loss of 1438 ml.

Discussion

Previous reports on measured blood loss at caesarean section were based on groups of patients who were more heterogeneous than those in our study and the methods used to measure blood loss were not necessarily accurate. Dieckman & Daily (1935) found that the mean measured blood loss in 20 patients was 539 ml. They did not mention the type of anaesthesia used. Three of the operations were performed for placental abruption and five other emergency operations were performed during labour. The investigators used sponges soaked in acid and wrung out the fluid in the sponges by hand. Dieckman & Stout (1950) reported a mean blood loss of 618 ml in six patients who were delivered by caesarean section under spinal anaesthesia. Tatum (1953) investigated eight patients of whom one had an emergency caesarean section. Most of the oper-

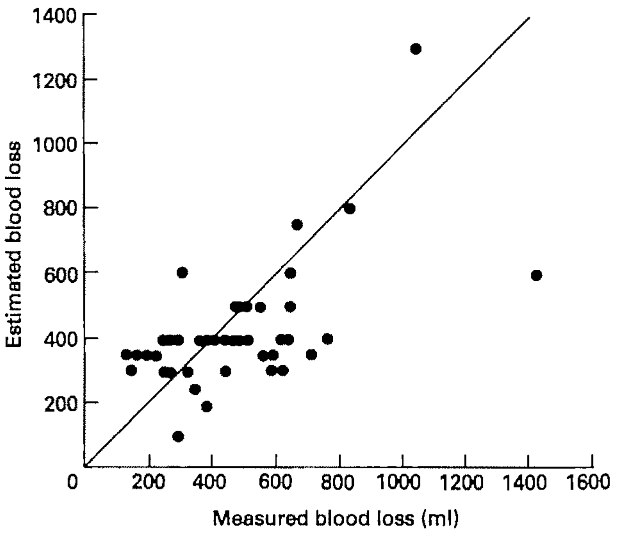

Fig. 1. Relation between estimated and measured blood loss at lower segment caesarean section. The line represents values where measured blood loss equals estimated blood loss.

ations used local anaesthesia—a practice which is rarely used now. Using serial plasma volume measurements Tatum (1953) reported an average blood loss of 923 ml. Wilcox *et al.* (1959) reported an average blood loss of 1028 ml in 25 sections of which six were classical caesarean sections, four were emergency caesarean sections and four were undertaken between 32 and 36 weeks gestation. More recently, Pritchard (1962) studied 40 patients using ^{51}Cr-labelled red blood cells and estimated, without reference to details of surgical technique, oxytocics, the surgeon's level of training or duration of the operation, that the average blood loss at caesarean section was 930 ml. Ueland (1976) estimated a mean decrease of 1030 ml in blood volume from the start of the operation to one hour postpartum.

Brant (1966) distinguished between elective and emergency caesarean sections and he measured blood loss meticulously in both situations. The average measured blood loss was 1068 ml in 22 elective sections and 1106 ml in 14 emergency sections. Ten of the 22 women delivered by elective section required blood transfusions either during or after the operation compared with only one of the 40 women in our study. An important finding in the study by Brant (1966) was that the surgeon under-estimated the volume of blood loss in 17 of the 20 elective sections where blood loss was estimated and in 13 of the 14 emergency sections.

The ability of pregnant women to withstand blood loss at delivery is related to their blood volume and haemoglobin level, the volume of blood loss and any associated complications. There are large variations in the blood volume at term (Cope 1958), even when height and body weight are taken into account (Hytten & Paintin 1963). The prevention and management of anaemia and any other pregnancy associated complications are among the fundamental objectives of antenatal care. Accurate estimation of the volume of obstetric haemorrhage is also very important (Brant 1966; Brant 1967; Anonymous 1967). Because of the dispersion of blood lost at caesarean section, accurate estimation is often difficult (Wilcox 1959). We have shown that the difference between measured and estimated blood loss increases when the measured loss exceeds 600 ml, and also if the measured blood loss is <400 ml there is a tendency to over-estimate the volume of loss.

It has been shown that use of the pre-operative 'type and screen' procedure, instead of cross-matching, reduces the cross-match to transfusion ratio and decreases costs (Ness *et al.* 1981; Reisner 1983). We would view such reports with caution and advocate that blood is fully cross-matched and available at all caesarean sections. The measured intra-operative blood loss was <500 ml in most of our patients but it was >750 ml in four (10%), >1000 ml in two (5%) and almost 1500 ml in one of them. Furthermore, blood loss at caesarean section is acute. We found that much of the blood loss took place between the time of incision and repair of the uterus but it was not possible, for practical reasons, to measure blood loss

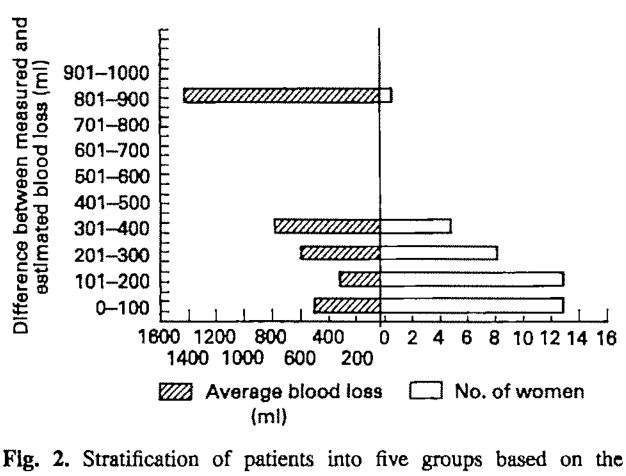

Fig. 2. Stratification of patients into five groups based on the difference between measured and estimated blood loss. The figure shows the difference between measured and estimated blood loss plotted against the average blood loss for each of the five groups and the number of patients in each group.

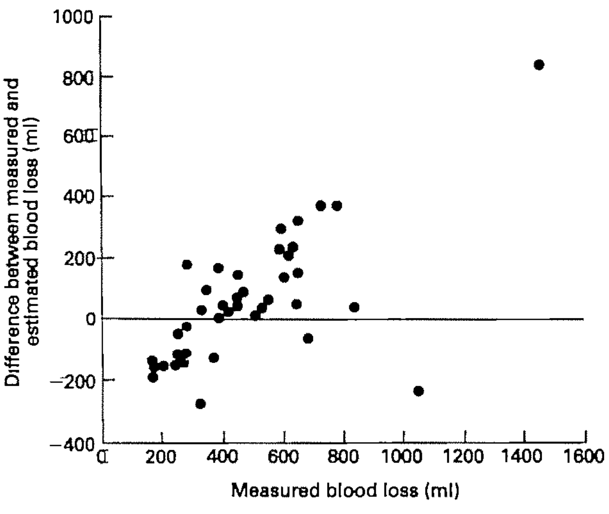

Fig. 3. Difference between measured and estimated blood loss related to measured blood loss.

from the uterus and from the anterior abdominal wall separately.

The availability of blood for obstetric patients is potentially life saving (Stallworthy 1939) and it is noteworthy that the triennial confidential enquiries into maternal deaths in England and Wales have consistently reported that haemorrhage following caesarean section is an important cause of maternal death (Department of Health 1991). In Hong Kong obstetric haemorrhage was the leading cause of maternal deaths between 1961 and 1985 (Duthie *et al.* 1989). Whilst we acknowledge that there are also risks associated with an allogenic blood transfusion (Roath 1991) we reiterate that cross-matched blood should be available during an elective or emergency caesarean section.

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Received 20 June 1991
Accepted 20 January 1992

British Journal of Obstetrics and Gynaecology
May 1992, Vol 99, pp. 368–370

OBSTETRICS

Thyroxine dosage during pregnancy in women with primary hypothyroidism

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ABSTRACT

Objective To assess whether pregnancy changes the thyroxine requirements of hypothyroid women.

Design A retrospective, longitudinal study.

Setting Queen Charlotte's and Chelsea Hospital for Women.

Subjects 32 women referred for antenatal care during 35 pregnancies.

Main outcome measures Changes in thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels as pregnancy progresses.

Results In most of the pregnancies (80%), no change in thyroxine dose was required (mean dose 129 µg). The mean TSH levels in early (1·8 mU/l) and in late pregnancy (1·5 mU/l) were unchanged ($P>0·5$). In the remaining pregnancies, thyroxine dose was increased after the first antenatal clinic appointment, on the basis of thyroid function test results, from a mean of 104 µg to a mean of 172 µg ($P<0·01$). These women had a mean early pregnancy TSH of 12·3 mU/l, which decreased by 95% to 1·3 mU/l ($P<0·01$).

Conclusions Most of the hypothyroid patients presenting to an antenatal booking clinic are well controlled in early pregnancy and will remain so throughout pregnancy. The dose of thyroxine does not need to be changed, and further assessments of thyroid function should not be necessary. It is unlikely that the patients were all 'over-treated' before conception, since they were referred to us by a large number of independent doctors. Women who are under-treated before the pregnancy are likely to require both increased thyroxine dose and further thyroid function assays. They can generally be easily detected, biochemically, at the first hospital visit.

Considerable debate and controversy surrounds the management of pregnant women with hypothyroidism. Many undergo frequent thyroid function tests because their doctors are unsure whether they need to increase the dose of thyroxine.

Hypothyroidism occurs in about 6 per 1000 pregnancies (Niswander & Gordon 1972). Recommendations regarding changes in dose of thyroxine during pregnancy are varied. Kaplan (1985) suggests that a woman who is well controlled before pregnancy will need an increase of 25–50 µg thyroxine per day, but goes on to state that in his experience most remain euthyroid on an unchanged dose. Similarly, Burrow (1988) concluded that the dose of thyroxine needed to be increased by 50–100 µg per day.

Pekonen *et al.* (1984) suggested that 8 out of 37 (22%) hypothyroid pregnant women need an increased dose of thyroxine, but the timing of the increase and the cause of hypothyroidism were not disclosed. In Japan, Tamaki *et al.* (1990) found that five pregnant women on suppressive doses of thyroxine following thyroid carcinoma needed increased doses.

The authors of a recent survey of 12 pregnant women concluded that 75% needed an increase in dose, mainly on the basis of thyroid stimulating hormone (TSH) levels, and that in all of these the dose could be returned to the previous level after delivery. Two of the remaining three women were felt to have been on an excessive dose before the pregnancy (Mandel *et al.* 1990).

The importance of correct management of hypothyroidism in pregnancy has been emphasised previously by Man (1975) who noted increased frequencies of perinatal mortality, and congenital and developmental anomalies. Although this is not accepted by all authorities, it seems sensible to optimise therapy and therefore minimise risk.

Our impression was that most women required no change in dose of thyroxine throughout pregnancy. Consequently we reviewed the thyroid function tests and thyroxine doses for all such patients. The majority were assessed retrospectively although a few who were identified during the study were followed prospectively.

Subjects and methods

The records of pregnant women with primary hypothyroidism

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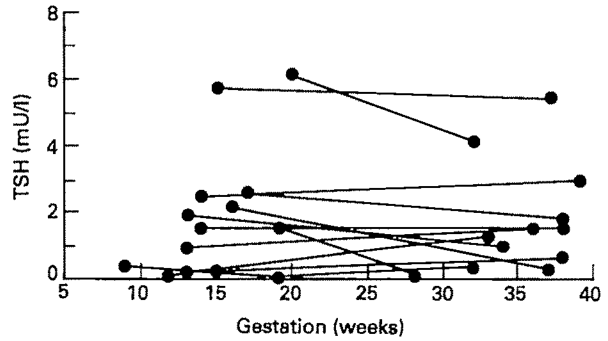

Fig. 1. Thyroid stimulating hormone (TSH) values in early and late pregnancy in 14 hypothyroid women whose daily thyroxine was not changed. Two values in early pregnancy just above normal range, but fT4 within normal range. (In both Figs 1 and 2 each woman is represented by one line, normal TSH values 0·4–4·0 mU/l).

were identified using the hospital computer to access thyroid function tests results and the database of the 'medical disorders in pregnancy' clinic. Our hospital caters for obstetrics and gynaecological patients only, and all women were previously under the care of their general practitioners or of a large number of hospitals in the London area. During the pregnancy, thyroid disease was managed in all cases by one of us (M. de S.).

During the period January 1987 to December 1990, 33 women with treated hypothyroidism had 37 pregnancies. All but one had taken thyroid replacement hormone before conception in the form of L-thyroxine (T4); the one woman took a mixture of T4 and triiodothyronine during two pregnancies, and was excluded from the analysis.

Thyroid function was assessed at least twice in all the women, usually at their first antenatal clinic visit and at 36 weeks gestation. When more than two sets of results were available, comparison was made between the first, and the highest TSH or lowest free thyroxine (fT4) levels to emphasize any tendency towards hypothyroidism induced by pregnancy.

Hormonal assay

A radioimmunoassay kit was used for fT4, and a immunoradiometric assay for TSH. The normal range for TSH is 0·4–4·0 mU/l. The normal range of fT4 in pregnancy is controversial, but most workers find that fT4 falls as pregnancy progresses, a representative range being 11–23 pmol/l (non pregnant), 11–22 pmol/l (first trimester), 11–19 pmol/l (second trimester), and 7–15 pmol/l (third trimester) (Parker 1985).

Statistical analysis

The levels of TSH and fT4 were not normally distributed, and so early and late pregnancy values were compared using Wilcoxon's signed-rank test.

Standard deviation and standard error of the mean were used to compare the thyroxine doses.

Results

The mean age of the women studied was 32·3 years (range 19·3–38·8 years), and the mean duration of hypothyroidism at conception was 7·6 years (range 1–30 years). The cause of hypothyroidism, where this could be identified, was Hashimoto's thyroiditis in 18 and thyroidectomy in nine (three for thyrotoxicosis, one for pressure symptoms, and five unspecified). None had had thyroid carcinoma, and thus all women were on replacement and not suppressive doses of thyroxine.

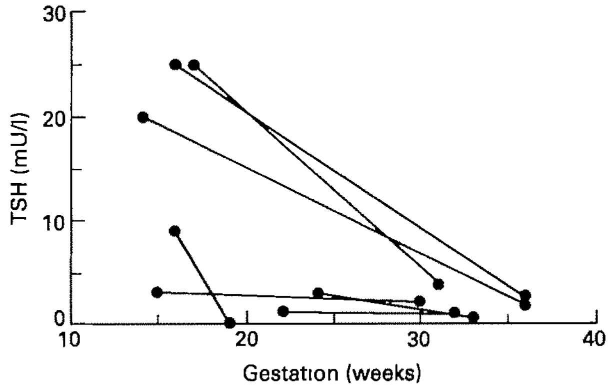

Fig. 2. TSH values in early and late pregnancy in seven hypothyroid women needing an increased amount of thyroxine.

All were well and had uncomplicated pregnancies. They were taking no other medication, apart from routine iron and folic acid supplements.

All changes in dose were made on the results of the thyroid function tests, except for one patient who became clinically hypothyroid, and one who became clinically hyperthyroid (see below).

Women requiring no change in dose of thyroxine (Fig. 1)

In 27 of the 34 pregnancies (80%), the women remained clinically and biochemically euthyroid, although in three either TSH or fT4 results were incomplete, or only total thyroxine values were available. In two, TSH levels at the first antenatal visit were just above the normal range (Fig. 1). However, in both of these, the fT4 was well within the normal range (17·0 pmol/l and 12·6 pmol/l in the second trimester) and the women were not clinically hypothyroid, and therefore the thyroxine dose was not altered.

The mean TSH was 1·8 mU/l in early pregnancy and 1·5 mU/l in late pregnancy, a non-significant decrease rather than any increase. The corresponding mean fT4 values were 18·8 pmol/l and 17·8 pmol/l (NS, $P>0{\cdot}5$) (Table 1). Five postnatal results were available, which showed that these women remained euthyroid after delivery (mean TSH 1·3 mU/l, mean fT4 20·2 pmol/l).

Women requiring increased doses of thyroxine (Fig. 2)

In eight pregnancies thyroxine dose was increased after the first antenatal appointment. In one it was subsequently reduced to the pre-pregnancy level when symptoms of hyperthyroidism developed. This patient was excluded from further analysis.

In this group of women who had their dose of thyroxine increased, the mean TSH in early pregnancy was 12·3 mU/l but this had decreased by 95% to a mean of 1·3 mU/l (in the normal

Table 1. Thyroid stimulating hormone (TSH), free thyroxine (fT4) and thyroxine dose (T4) in early and late pregnancy in women with primary hypothyroidism

	Early pregnancy			Late pregnancy		
Patient group	TSH (mU/l)	fT4 (pmol/l)	T4 (μg)	TSH (mU/l)	fT4 (pmol/l)	T4 (μg)
Dose unchanged	1·8 (0–6·1) (n = 14)	18·8 (12–25) (n = 22)	129 (25–200) (n = 27)	1·5 (0–5·4) (n = 14)	17·8 (12–27) (n = 22)	129 (25–200) (n = 27)
Dose changed	12·3 (3–25) (n = 7)	12·1 (9–17)†† (n = 6)	104 (50–175)** (n = 7)	1·3 (0·1–4)† (n = 7)	14·4 (9–22) (n = 6)	172 (100–250)* (n = 7)

Results are mean values with range in parenthesis, n gives the number of women in each group (all data are paired).

*$P<0{\cdot}01$ for comparison with values of thyroxine dose in early pregnancy

**$0{\cdot}5>P>0{\cdot}1$ for comparison with values of thyroxine dose in group with no change.

†$P<0{\cdot}01$ for comparison with values of TSH in early pregnancy.

††$P<0{\cdot}01$ for comparison with values of fT4 in group with no change.

range) when next assessed, indicating improved control. In three of these women, postnatal results were available, showing that all remained well controlled on the same, increased, dose (mean TSH 1·7 mU/l and mean fT4 25 pmol/l). This included one woman who had been diagnosed relatively recently, and had had her thyroxine dose increased 6 weeks before conception; she subsequently required a further increase in early pregnancy.

Changes in thyroxine dose

The mean daily thyroxine dose for the group whose requirement did not change was 129 μg (SD48·6, range 25–200). In the other group whose requirement increased, the mean basic daily dose was 104 μg (SD46·6, range 50–175), and this was increased to a mean dose of 172 μg (SD56·7, range 100–250). This increase in dose was significant $P<0{\cdot}01$). There was, however, no significant difference in the daily dose in early pregnancy between the two groups ($0{\cdot}5>P>0{\cdot}1$).

Discussion

We have shown that most women with hypothyroidism are well controlled by their prepregnancy treatment at the first antenatal clinic visit and can be expected to remain euthyroid throughout pregnancy without alteration in the requirement for thyroxine. The minority who needed their thyroxine dose increased were all detected biochemically at their first hospital visit. No further changes in dose were necessary in this group and they remained on the higher dose post-partum. Thus, it seems that these changes in the dose of thyroxine were a consequence of under-treatment before conception, rather than a reflection of increasing demand for thyroxine with advancing pregnancy.

Prepregnancy thyroid function tests were not available to us, and therefore there was no definite evidence that all the women were truly hypothyroid. However, a large number of doctors referred these patients to us, and it is unlikely that they were all being unnecessarily treated. In addition, in 25 of 27 pregnancies in which the thyroxine dose was not changed, women were taking the usual maintenance dose of 100–200 μg daily, (British National Formulary 1990), and all were clinically euthyroid. By the same reasoning, it is also unlikely that 'over-treatment' before conception resulted in stable doses during pregnancy. Our experience relates to the management of treated hypothyroidism as it presents in a busy obstetric hospital.

In general, patients were well motivated, and had a good understanding of their disease. Compliance was therefore judged to be good. If, however, this was an overestimation of the situation, and patients were taking less thyroxine than intended, it would only strengthen our proposal that an increased dose is not necessary.

We believe that all hypothyroid women should have TSH and fT4 estimated in early pregnancy. or before conception if possible. Subsequent laboratory assessment is only required if clinically indicated or during thyroxine dose adjustment.

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Received 24 June 1991
Accepted 29 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 371–376

OBSTETRICS

A randomized placebo-controlled study of the effect of low dose aspirin on platelet reactivity and serum thromboxane B_2 production in non-pregnant women, in normal pregnancy, and in gestational hypertension

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ABSTRACT

Objective To investigate the effect of 60 mg aspirin daily on platelet reactivity and prostaglandin production in various groups of patients. Similar regimens, which are thought to act through inhibition of platelet thromboxane production, are currently undergoing clinical assessment for the prevention of pre-eclampsia and intrauterine growth retardation.

Design A prospective randomized placebo controlled study.

Setting University Hospital, Nottingham.

Subjects 12 non-pregnant female volunteers, 18 normal primigravidae before 16 weeks gestation and 16 pregnant women admitted with gestational hypertension (GH) at a mean gestation of 38 weeks.

Interventions In the non-pregnant women blood samples were taken before and after a 10-day course of 60 mg aspirin daily. The primigravidae had blood samples taken at 16 weeks and then they were randomized to receive either 60 mg aspirin daily or a matched placebo. Further blood samples were obtained at 28, 32 and 36 weeks.

Main outcome measures Changes in platelet reactivity and release reaction, and serum thromboxane production, were estimated in whole blood.

Results 60 mg aspirin daily significantly inhibited cyclo-oxygenase dependent platelet aggregation, release reaction and serum thromboxane production in non-pregnant and pregnant women, and in women with GH ($P<0{\cdot}01$). When adrenaline was used as the aggregating agent, the cyclo-oxygenase pathway was recruited in the increased reactivity seen in the third trimester of normal pregnancy, and was sensitive to inhibition by low dose aspirin.

Conclusion Low dose aspirin would appear to be an appropriate agent for the inhibition of platelet reactivity associated with hypertensive pregnancy.

Several small studies have shown that low doses of aspirin may prevent pre-eclampsia in selected patients (Beaufils *et al.* 1985; Wallenburg *et al.* 1986; Schiff *et al.* 1989). Aspirin acts via the irreversible acetylation of the platelet enzyme cyclo-oxygenase, which is responsible for the synthesis of thromboxane A_2 (TxA_2) by platelets. TxA_2 is a powerful vasoconstrictor and potent promoter of platelet aggregation, and increased amounts have been found in women with pre-eclampsia (Greer *et al.* 1985a; Fitzgerald *et al.* 1990). The imbalance between this excess and the relative failure of prostacyclin synthesis (Walsh *et al.* 1985; Greer *et al.* 1985a; Fitzgerald *et al.* 1987), along with platelet activation, has been implicated in the pathogenesis of pre-eclampsia (Wallenburg 1986).

We have studied the effect of 60 mg aspirin daily on platelet reactivity and serum thromboxane production in non-pregnant women, normal pregnant women, and women with gestational hypertension (GH), to determine the effectiveness of this regimen in the inhibition of platelet cyclo-oxygenase, and to assess its ability to restore the balance between the opposing

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Table 1. Clinical characteristics of the two pregnant study groups

	Normal primigravidae (*n*=18)		GH group (*n*=16)	
	Placebo	Aspirin	Placebo	Aspirin
Age (years)	26 (4)	22 (3)	24 (5)	23 (3)
Gestational age at recruitment (weeks)	16 (2)	16 (2)	37·0 (1·9)*	39·5 (0·8)
Weight at 16 weeks (kg)	65 (11)	64 (15)	67 (13)	67 (16)
Blood pressure at recruitment (mm Hg)	111/66 (9)/(8)	114/68 (9)/(7)	146/96 (9)/(8)	143/95 (6)/(6)
Serum urate at recruitment (μmol/l)	–	–	309 (70)	297 (74)
Gestational age at delivery (weeks)	40 (1·5)	40 (1·7)	37 (1·4)	39 (1·2)
Proteinuria (g/24 h)	–	–	–	0·6 (0·7)
Birthweight (kg)	3·3 (0·4)	3·3 (0·6)	2·6 (0·7)*	3·5 (0·5)
Birthweight <10th centile	0	0	1	1
Duration of labour (h)	9 (3)	7 (3)	7 (3)	9 (4)
Estimated blood loss at delivery (ml)	215 (122)	335 (101)	226 (169)	325 (150)
Minor bruising in newborn	1	2	4	3

Results are mean (SD) values.
*There was a significant difference ($P<0·05$) in gestational age at recruitment and birthweight between the placebo and aspirin arms in the gestational hypertension group.

actions of thromboxane and prostacyclin. We have used whole blood techniques which avoid the centrifugation step required in the preparation of platelet-rich plasma, the medium which has been most widely used in past studies of platelet reactivity (Howie *et al.* 1971; Hoche *et al.* 1983; Morrison *et al.* 1985). As centrifugation removes both the largest and most active platelets from the study medium, and also red and white blood cells which are known to influence platelet behaviour (Gaarder *et al.* 1961; Blackwell *et al.* 1978), we believe that the study of platelets in their natural milieu of whole blood is a more physiological technique, and more closely reflects the *in vivo* situation.

Subjects and methods

Three groups of subjects were studied. The first group included 12 non-pregnant female volunteers (mean age 27, SD 4 years) who were recruited from the hospital staff. None of these women was using oral contraception. Blood samples were taken before and after a 10-day course of 60 mg aspirin daily. The second group included 18 normal primigravidae (mean age 24, SD 5 years) who were recruited from the antenatal booking clinic at 16 weeks gestation, and these subjects were simply randomized with block size four, to receive either 60 mg aspirin (*n*=10), or identical placebo (*n*=8), daily until delivery. Blood samples were taken before randomization, and repeated at 28, 32 and 36 weeks gestation, and at 6 and 12 weeks after delivery. The third group included 16 primigravidae (mean age 23, SD 4 years) who were recruited after admission to hospital with a diagnosis of GH. This was defined as a blood pressure of at least 140/90 mmHg on two occasions 24 h apart, after 20 weeks gestation in a previously normotensive woman, and in whom the blood pressure returned to normal within 3 months of delivery. Patients with significant proteinuria (>0·5 g/24 h) were excluded, as many of these patients were delivered electively shortly after admission. The 16 women with GH were also randomized to receive either 60 mg aspirin (*n*=8) or placebo (*n*=8) daily until delivery. None of the pregnancies was complicated by essential hypertension, renal disease or use of drugs known to influence platelet behaviour. Informed consent was obtained in all cases.

A paediatrician who was unaware of the treatment allocation examined the infants 1 or 2 days after birth. Assessment was made of any stigmata of increased bleeding tendency, including bruising, petechiae, cephalhaematoma and bleeding from the umbilical cord stump. Blood loss at delivery was estimated by a clinician (K.A.L.) on clinical grounds only.

Experimental technique

Blood collection was undertaken as decribed previously (Louden *et al.* 1990) as were platelet aggregation, release reaction and serum TxB_2 production measurements. In brief, platelet aggregation was measured using a single platelet counting technique after the addition of a bolus of one of the aggregating agents. The six aggregating agents employed, at the final concentrations in whole blood, were: arachidonic acid (0·2 mM), adrenaline (1 μM), adenosine diphosphate (ADP, 0·5 μM), platelet activating factor (0·03 μM), collagen (1 μg/ml) and U46619 (a synthetic thromboxane mimetic, 0·3 μM). The Sigma Chemical Company supplied the arachidonic acid, adrenaline, ADP, and platelet activating factor, whilst the collagen was obtained from Horm Chemicals, Munich, and the U46619 was supplied by the Upjohn Co., Kalamazoo, Michigan, USA.

Table 2. Effect of aspirin treatment on platelet aggregation and release reaction in 12 normal non-pregnant women

	Before aspirin Median (quartiles)	After aspirin Median (quartiles)
AA-induced platelet aggregation (after 4 min) (%)	90 (28,95)	28 (24,35)
AA-induced release reaction (%)	29 (7,37)	0 (0,1)
Collagen-induced platelet aggregation (after 1 min) (%)	94 (93,95)	69 (60,82)
Collagen-induced release reaction (%)	25 (19,28)	2 (1,5)

There was a significant reduction ($P<0·01$) both in platelet aggregation and release reaction after aspirin treatment.
AA=arachidonic acid.

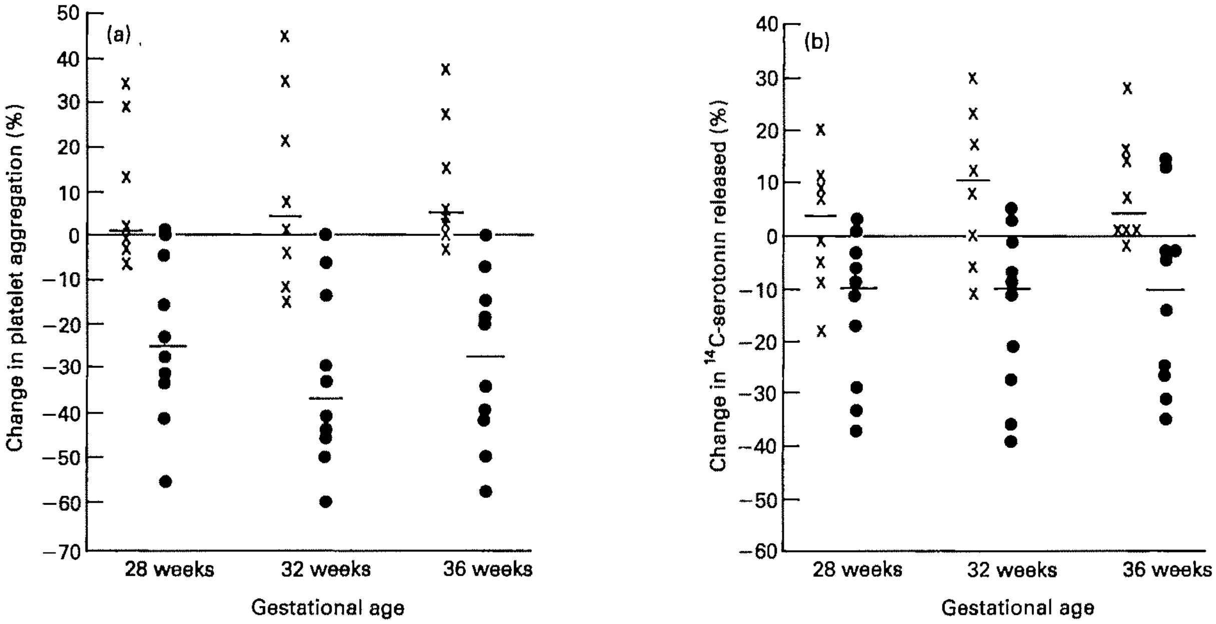

Fig. 1. The effect of low-dose aspirin on the percentage change in arachidonic acid induced platelet aggregation (a) and release reaction (b) from pretreatment values at 16 weeks to 28, 32, 36 weeks during normal primigravid pregnancy (placebo (×) n=8, aspirin (●) n=10). Significant inhibition (P<0·01) after aspirin was noted on all three occasions for platelet aggregation, and at 32 and 36 weeks for release reaction. Median values are shown.

The fall in the single free platelet count was measured using the Clay Adams Ultra Flo 100 counter, to give the proportion of aggregated platelets. Values were obtained at 10 s intervals for the first minute after addition of the aggregating agent, and also after 2, 4 and 8 min. The release reaction was quantified by measurement of the amount of radio-label released following the aggregation of platelets as described for platelet aggregation, when the platelets had been pre-incubated with ^{14}C-labelled serotonin, which is taken up into platelet storage granules. The serum production of TxB_2, the major stable metabolite of TxA_2, was measured using a radio-immunoassay kit (Amersham International plc, Amersham, UK), following spontaneous clotting at 37°C for 1 h.

Statistical analysis

As the sample size was small, and the experimental data tended not to be normally distributed, medians have been used as the estimate of central tendency, and 25th and 75th centiles have been used as estimates of the scatter of the data. When such values appear in the text, they have been expressed as (median, 25th, 75th centile). Wilcoxon paired rank sum tests (paired data) and Mann-Whitney U tests (unpaired data) were performed, thereby avoiding assumptions with regard to the distribution of the data. This test was employed because no unpaired non-parametric analysis of variance with repeated measures could be identified. As a consequence, the arbitrary level of statistical significance has been adjusted from P<0·05 to P<0·01, to account for the increased number of statistical tests performed on the experimental data.

Results

Clinical

The aspirin and placebo groups of both the normal primigravidae and the patients with GH were well matched for age, weight and blood pressure (Table 1). In the GH group, the patients who received aspirin were recruited at a significantly more advanced gestational age than those who received placebo (P<0·05, Table 1).

Mean birthweight was significantly higher in the patients with GH who received aspirin compared with those who received placebo (P<0·05, Table 1). None of the women was delivered before 36 weeks gestation. None of the women in the normal pregnancy group developed GH or gave birth to a low birthweight baby, but two infants in the GH group weighed less than the 10th centile for gestational age (one each in the aspirin and placebo arms). Four of the eight women in the placebo arm of the GH group developed significant proteinuria (>0·5g/24 h) before labour, whereas none in the aspirin arm did so. Estimated blood loss at delivery was not significantly increased in the women who received low-dose aspirin, in comparison with those who received placebo, although higher mean values were noted. One normal primigravida assigned to placebo complained or rectal bleeding at 32 weeks; this was ascribed to haemorrhoids. No differences in neonatal bleeding tendency were detected between the infants exposed to maternal aspirin and maternal placebo. These results are summarized in Table 1.

Platelet reactivity

Both arachidonic acid and collagen-induced platelet aggrega-

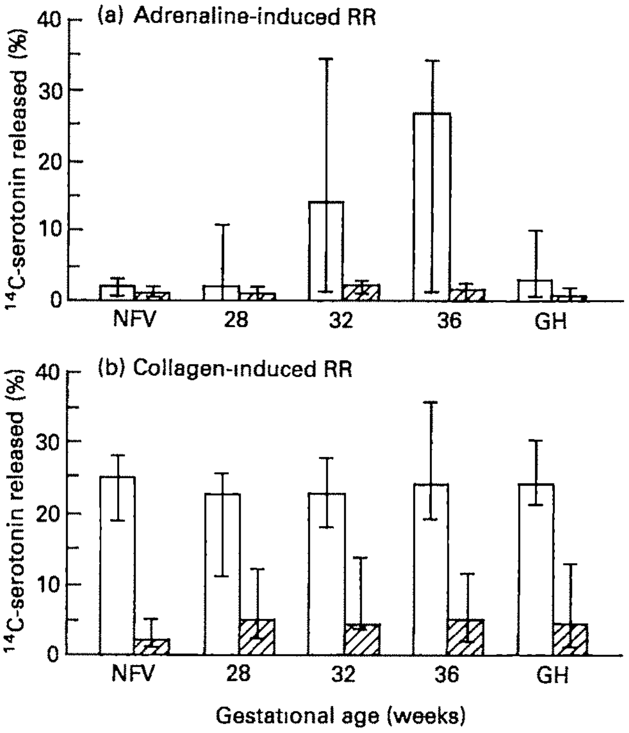

Fig. 2. (a) The effect of low-dose aspirin on adrenaline-induced release reaction (RR) in the three study groups (i) normal female volunteers (NFV) (n=12); (ii) normal pregnancy measured at 28, 32 and 36 weeks gestation (n=18); (iii) gestational hypertension (GH) (n=16). Significant ($P<0\cdot01$) inhibition of release reaction was seen at 36 weeks. ☐ placebo; ▨ aspirin.

(b) This similar figure refers to collagen-induced release reaction (RR). Significant ($P<0\cdot01$) inhibition was seen at 32 and 36 weeks Median values and quartiles are shown.

tion and release reaction were significantly inhibited 10 days after ingestion of 60 mg aspirin daily ($P<0\cdot01$) in the non-pregnant women. Results are shown in Table 2. The choice of 4 min (for arachidonic acid) and 1 min (for collagen) time points coincided with the time of maximum aggregation for each of these aggregating agents. In addition to spontaneous (saline-induced) platelet aggregation, the responses to adrenaline, ADP, platelet aggregating factor and U46619-induced platelet aggregation and release reaction were unchanged after low-dose aspirin.

Table 3. Effect of aspirin treatment on platelet aggregation and release reaction in 16 women with gestational hypertension (GH)

	Placebo group (n=8) Median (quartiles)	Aspirin group (n=8) Median (quartiles)
AA-induced platelet aggregation (after 4 min) (%)	95 (94,96)	46 (20,48)
AA-induced release reaction (%)	33 (23,35)	1 (0,13)
Collagen-induced platelet aggregation (after 1 min) (%)	89 (74,92)	59 (52,90)
Collagen-induced release reaction (%)	24 (22,30)	4 (1,13)

There was a significant reduction both in induced-platelet aggregation and release reaction ($P<0\cdot01$) after treatment with low-dose aspirin in women with GH.
AA=arachidonic acid.

Despite the randomization procedure, the group of normal primigravidae randomized to receive aspirin had a lower initial arachidonic acid induced platelet aggregation at 16 weeks (median 62%. interquartile range 34, 79) than those randomized to receive placebo (median 92%, interquartile range 48, 94) and a lower release raction (median 11%, interquartile range 2, 33) compared with those randomized to receive placebo (median 27%, interquartile range 0, 34). Although neither of these differences was statistically significant ($P>0\cdot05$ in each case), it was felt that it was of sufficient magnitude to render direct comparison of the two groups invalid. Thus, for this aggregating agent, comparisons were drawn between the *change* in platelet aggregation from pre-treatment to post-treatment values.

The change in arachidonic acid induced platelet aggregation and release reaction from pre-treatment, at 16 weeks, to 32 and 36 weeks, showed significant inhibition after low-dose aspirin ($P<0\cdot01$ in each case). The change from 16 to 28 weeks showed significant inhibition for platelet aggregation only (Figs. 1a and 1b). Direct comparison of both adrenaline and collagen-induced platelet aggregation also showed significant inhibition in the aspirin-exposed group at 28 weeks ($P<0\cdot01$), but this inhibition was less marked and not significant at 32 and 36 weeks. Adrenaline-induced release reaction was significantly reduced in the aspirin group at 36 weeks, whilst collagen-induced release reaction was significantly reduced at both 32 and 36 weeks ($P<0\cdot01$ in each case) (Figs. 2a and 2b). Figure 2a also illustrates the increase in adrenaline-induced release reaction over the course of the pregnancy in the placebo group. Low-dose aspirin did not significantly inhibit platelet aggregation induced by saline, ADP, platelet aggregating factor or U46619.

In the patients with gestational hypertension, both arachidonic acid and collagen-induced platelet aggregation and release reaction were significantly inhibited after low-dose aspirin ($P<0\cdot01$, Table 3). No significant inhibition of the responses to saline, adrenaline (Fig. 2a), ADP, platelet aggregating factor, or U46619-induced platelet aggregation or release reaction were seen. These studies were performed at an average of 38 weeks and 2 days. A mean of 9 treatment days elapsed before delivery, and all patients received at least 3 days of treatment. No samples were taken from patients in labour.

Figure 3 (a and b) illustrates the change in arachidonic acid and collagen-induced platelet aggregation and release reaction from before treatment to after treatment, comparing the placebo and aspirin groups. This is included to allow comparisons to be drawn between the effect of aspirin on platelet reactivity in patients with gestational hypertension (Figs. 3a and 3b) and normal pregnancy (Figs. 1a and 1b).

Serum TxB_2 production

Serum TxB_2 production was significantly reduced after low-dose aspirin in all cases. The results are shown in Fig. 4. Results are expressed as median (quartiles) nmol $TxB_2/10^9$ platelets.

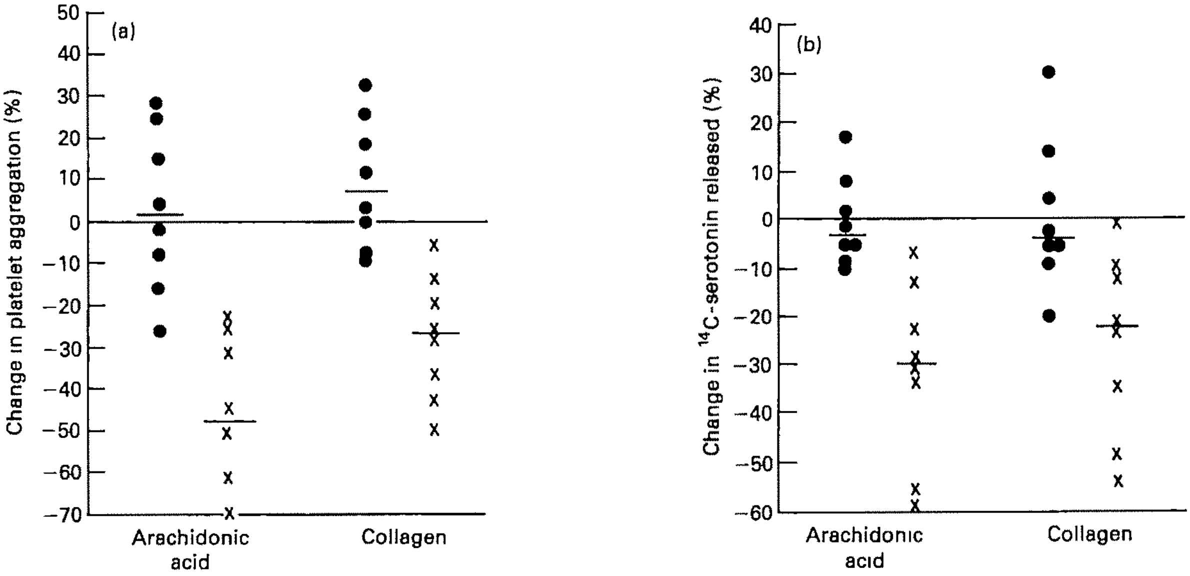

Fig. 3. The effect of low-dose aspirin on percentage change in arachidonic acid and collagen-induced platelet aggregation (a) and release reaction (b) in 16 patients with gestational hypertension. Significant inhibition ($P<0{\cdot}01$) after aspirin was seen in each case. Median values are shown. ● before aspirin; × after aspirin.

Discussion

The inhibitory effect of low-dose aspirin on platelet reactivity (Carter & Heptinstall 1985) and thromboxane synthesis (Toivanen 1984) has been reported previously in whole blood, but this is the first study to examine such effects in pregnant women. Our studies have shown that even with 60 mg aspirin daily, the dose currently undergoing clinical assessment in the 'collaborative low-dose aspirin studies in pregnancy' (CLASP), significant inhibition of arachidonic acid-induced, and therefore cyclo-oxygenase dependent, platelet reactivity may be achieved in non-pregnant and pregnant women, and patients with gestational hypertension. We have also demonstrated a correspondingly consistent pattern of inhibition of median serum TxB_2 production of the order of 90% in these patients.

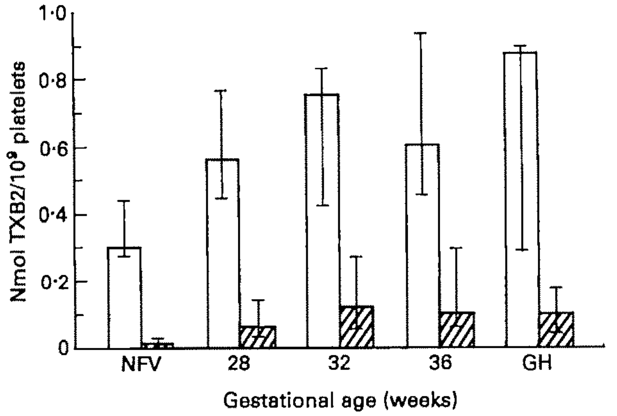

Fig. 4. Inhibition of serum thromboxane B_2 (TxB_2) production after low-dose aspirin, in the three study groups (i) NFV=non pregnant female volunteers; (ii) normal pregnancy measured at 28, 32 and 36 weeks; (iii) gestational hypertension (GH). Median values and quartiles are shown. There was a significant inhibition in each of the study groups ($P<0{\cdot}01$) □ placebo; ▨ aspirin.

In those instances in which platelet reactivity is inhibited by aspirin, TxA_2 prodution is presumably involved. Low-dose aspirin did not inhibit adrenaline-induced platelet reactivity in non-pregnant women, nor at 16 weeks gestation, but as adrenaline-induced platelet reactivity increased as pregnancy progressed, it was clear that this increase was inhibited by aspirin. It would therefore appear that the increased reactivity seen in normal primigravid pregnancy (Louden *et al.* 1990) is associated with increasing activity of the cyclo-oxygenase pathway, with the production of TxA_2. Although serum TxB_2 production appears to be unchanged in normal pregnancy (Louden *et al.* 1990), platelet thromboxane production measured by gas chromatography mass spectrometry of urinary metabolites, which is widely regarded as the 'gold standard', does appear to be increased towards term (Fitzgerald *et al.* 1987). It has been shown that beta-receptor blockers may inhibit platelet reactivity, but that this effect occurs because of a membrane stabilizing action rather than beta-receptor blockade (Greer *et al.* 1985b). This would suggest that the increase in platelet reactivity in normal pregnancy is not only dependent on the cyclo-oxygenase pathway, but perhaps also on an increase in the sensitivity of the platelet membrane. It may be that changes in platelet intracellular free calcium concentration, which rises towards term, could play a key role (Kilby *et al.* 1989). That we did not demonstrate inhibition of adrenaline-induced platelet reactivity by low-dose aspirin in the GH patients is a reflection of the reduction in median values compared with normal pregnancy, as we have described previously (Louden *et al.* 1991), which we believe reflects platelet 'exhaustion' in this condition.

In this very small study, we were unable to detect any side effects of low-dose aspirin in either mother or baby. This study was designed to measure changes in platelets and prostaglandins, rather than clinical outcomes. Obviously, the results of much larger studies will be required before any conclusions may be drawn, particularly with regard to blood loss at delivery, and the possibility of a neonatal bleeding tendency. Similarly, our observation of a reduction in the progression of GH to proteinuric pre-eclampsia remains of uncertain significance. It remains to be seen whether the ability of low-dose aspirin to inhibit platelet cyclo-oxygenase, which we have demonstrated in normal and hypertensive pregnancy, will be reflected by an improvement in perinatal mortality. We look forward to the publication of the results of several ongoing studies of this regimen in clinical practice.

Acknowledgments

We wish to thank Mrs M. Villiers for technical assistance, and Bristol Meyers Pharmaceuticals for the provision of the matched aspirin and placebo tablets. This study was supported by Trent Regional Health Authority.

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Received 28 December 1990
Accepted 12 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 377–380

OBSTETRICS

The characteristics of the second stage of labour in 25 069 singleton deliveries in the North West Thames Health Region, 1988

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ABSTRACT

Objective To define the contemporary characteristics of the second stage of labour in one Health Region.
Design Retrospective analysis of a regional obstetric database.
Setting Seventeen maternity units in the North West Thames Health Region.
Subjects Selected from 36 727 consecutive singleton deliveries in 1988. The analysis was confined to the 25 069 women delivered of an infant of at least 37 weeks gestation with a cephalic presentation following the spontaneous onset of labour.
Main outcome measures Second stage duration, obstetric intervention and maternal and fetal morbidity.
Results The duration of the second stage and the use of operative intervention were strongly negatively associated with parity and positively associated with the use of epidural analgesia. Maternal age, fetal birthweight and maternal height were also independently associated with the duration of the second stage. There were small but significant differences in the characteristics of women using epidural analgesia and those using alternative methods of pain relief. Parous women using epidural analgesia behaved in a similar manner to nulliparae without epidurals. Despite the longer second stages observed in women using epidural analgesia there appeared to be no significant increase in fetal morbidity. Within the region the epidural rate in individual units positively correlated with the overall forceps rate, the rate of caesarean section in the second stage of labour and the duration of the second stage.
Conclusions In our study the duration of the second stage in women not using epidural analgesia was similar to previous findings, but in those using epidural analgesia, the duration of the second stage was longer than has been reported previously, possibly reflecting a more conservative approach to operative intervention. Survival analysis indicates that in multiparae not using epidural analgesia the likelihood of spontaneous vaginal delivery after 1 h in the second stage was low, but in those multiparae using epidural analgesia and in all nulliparae there was no clear cut-off point for expectation of spontaneous delivery in the near future; they continue to give birth at a steady rate over several hours. While maternal and fetal conditions are satisfactory, intervention should be based on the rate of progress rather than the elapsed time since full cervical dilatation.

There is no satisfactory definition of normal labour and publications describing the characteristics of normal labour seldom use identical criteria when selecting a study population. The exclusion of women requiring instrumental delivery or oxytocin augmentation may allow the definition of a 'super-normal' cohort for analysis but this would fail to take into account what actually happens in practice. In addition, the outcome of labour will be determined in many respects by contemporary obstetric and analgesic policies and therefore the characteristics of labour in a defined population may vary as management strategies evolve. With these factors in mind the present study was undertaken to characterize second stage labour in one Regional Health Authority in 1988.

Subjects and methods

The St Mary's Maternity Information System is an on-line obstetric data collection system currently in use in all maternity units within the North West Thames Health Region of England. Data are collected prospectively from booking until 28 days after delivery. At the end of each year patient identifiers are removed and the total data set is transferred to the University of London Amdahl computer for statistical analysis. In the year ending December 1988, data were collected for

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Table 1. Median duration (with inter-quartile range) of the second stage of labour by parity and the use of epidural analgesia

	Duration of second stage (min)					
	Epidural analgesia			No epidural analgesia		
Parity	*n*	Median	IQ range	*n*	Median	IQ range
0	2662	82	(45–134)	8270	45	(27–76)
1	720	36	(20–77)	7871	15	(10–25)
2	191	25	(14–60)	3401	11	(7–20)
3	47	23	(12–53)	1151	10	(5–16)
≥4	20	22	(9–30)	736	10	(5–15)

IQ range = interquartile range.

36 727 singleton pregnancies from 17 units with between 858 and 4437 births each. These form the basis for this study, to define the contemporary characteristics of second stage labour.

In order to study a relatively homogeneous population the analysis was confined to women who had spontaneous onset of labour, reached the second stage of labour and were delivered of a singleton fetus of at least 37 weeks gestation with a cephalic presentation. The onset of the second stage was either the time at which full dilatation of the cervix was diagnosed on vaginal examination, or the time that the urge to bear down was accompanied by clinical signs of full dilatation of the cervix, whichever occurred first.

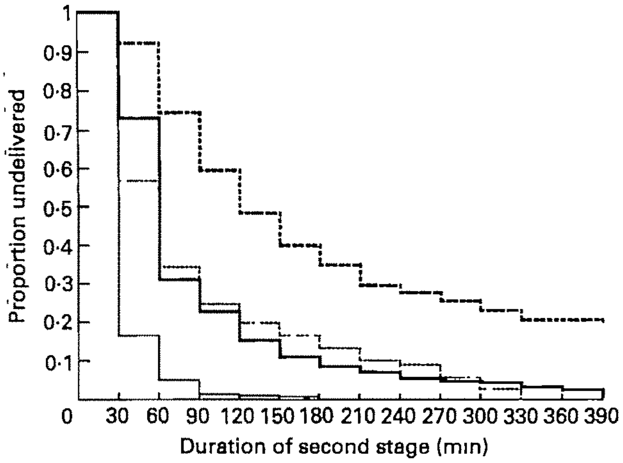

Fig. 1. Survival analysis of the duration of the second stage of labour. Nulliparous women are shown in bold on the graph, parous women in light. The dashed lines represent women with epidurals, the solid lines those without.

Statistical analysis

The 95% confidence intervals (CI) for differences in mean values and proportions were calculated using CIA software (Gardner *et al* 1989). All other analyses were performed using SAS (SAS Institute Inc 1985). Survival analysis was used to estimate the duration of the second stage without operative intervention and to assess the significance of factors associated with the duration of the second stage of labour.

Results

A total of 25 069 women satisfied the selection criteria for this

Table 2. Median duration (with interquartile range) of the second stage of labour (in min) by maternal age, birthweight and maternal height

	Nulliparae						Multiparae					
	Epidural			No epidural			Epidural			No epidural		
	n	Median	IQ range	*n*	Median	IQ range	*n*	Median	IQ range	*n*	Median	IQ range
Maternal age (years)												
<20	274	60	(35–104)	1072	34	(22–56)	10	22	(8–29)	219	10	(7–18)
20–24	764	72	(40–121)	2795	39	(25–66)	139	26	(15–48)	2469	12	(8–20)
25–29	1004	87	(49–135)	2922	49	(30–81)	346	30	(15–62)	4913	13	(8–21)
30–34	488	100	(56–152)	1192	57	(33–96)	315	36	(16–79)	3920	14	(8–23)
35–39	118	107	(68–166)	261	68	(35–110)	139	44	(22–85)	1369	15	(9–25)
40+	14	66	(44–120)	28	90	(52–154)	29	63	(20–128)	269	16	(10–31)
Birthweight (g)												
<2500	51	65	(25–100)	228	31	(20–54)	16	18	(8–38)	211	10	(6–15)
2500–2999	470	71	(36–120)	1700	35	(21–68)	133	28	(15–56)	1994	11	(7–19)
3000–3499	1187	77	(41–127)	3698	43	(26–74)	349	31	(17–67)	5295	13	(8–21)
3500–3999	736	95	(56–145)	2158	53	(32–89)	343	36	(20–78)	4188	14	(8–24)
4000–4500	195	114	(64–167)	438	64	(38–95)	122	35	(20–79)	1261	15	(10–26)
4500+	23	120	(62–167)	48	82	(56–120)	15	61	(17–137)	210	20	(11–34)
Maternal height (cm)												
<155	463	79	(40–125)	1362	42	(26–72)	158	40	(20–80)	219	10	(7–18)
155–159	529	85	(45–129)	1608	45	(27–77)	219	31	(18–69)	2469	8	(1–12)
160–164	717	82	(46–132)	2329	45	(27–75)	266	33	(18–75)	4913	13	(8–21)
165–169	582	80	(43–133)	1820	46	(27–78)	226	30	(16–59)	3920	16	(8–23)
170–174	279	90	(52–148)	899	44	(27–76)	80	37	(16–73)	1369	15	(9–25)
175+	92	95	(54–148)	252	48	(27–80)	29	24	(11–53)	269	16	(10–31)

IQ range = interquartile range.

Table 3. Maternal and fetal characteristics in nulliparae and multiparae with and without epidural analgesia

	Nulliparae			Multiparae		
	Epidural (n = 2662)	No epidural (n = 8270)	Difference (95% CI)	Epidural (n = 978)	No epidural (n = 13 159)	Difference (95% CI)
Maternal age (years)	26·5 (4·9)	25·6 (4·5)	0·9 (0·7 to 1·1)	30·1 (4·9)	29·3 (4·9)	0·8 (0·5 to 1·1)
Maternal height (cm)	162 (7)	162 (7)	0 (−0·3 to 0·3)	162 (7)	161 (7)	1 (0·5 to 1·5)
Birthweight (g)	3354 (443)	3298 (434)	56 (37 to 75)	3474 (470)	3429 (460)	45 (15 to 74)
Duration of second stage (min)	97 (68)	58 (46)	39 (37 to 41)	54 (55)	19 (21)	35 (33 to 37)
Mode of delivery (%)						
Spontaneous	57·8	86·7	−28·9 (−26·9 to −31·0)	82·2	98·1	−15·9 (−13·5 to −18·3)
Forceps	38·9	12·4	26·5 (24·5 to 28·5)	16·6	1·7	14·9 (12·5 to 17·2)
LSCS (2nd stage)	3·3	0·9	2·4 (1·7 to 3·2)	1·2	0·2	1·0 (0·3 to 2·2)
Episiotomy rate (%)	61	45	16 (14 to 18)	32	13	19 (16 to 22)

LSCS = lower segment caesarean section.

Results are mean (SD) values or proportions (%) as appropriate, differences are calculated between means or proportions as appropriate

study. Duration of the second stage was strongly associated with parity and the use of epidural analgesia (Table 1). Because of this the population was divided into four groups: nulliparae and multiparae with and without epidural analgesia. Only those women who had epidural analgesia for pain relief in the first stage of labour were included in the epidural groups. Duration of the second stage was also associated with maternal age, fetal birthweight and maternal height (Table 2).

The maternal characteristics of nulliparae and multiparae, with and without epidural analgesia are given in Table 3. It can be seen that epidural users were older with heavier babies; their length of the second stage was longer and a greater proportion required operative intervention.

Considering the probability of spontaneous vaginal delivery in relation to the duration of the second stage, allowance needs to be made for those women whose second stage has been terminated by operative delivery (Kadar 1986). Fig. 1 shows the duration of the second stage in half hour intervals in the four groups. Operative deliveries are censored (removed from the analysis) at the time of intervention. There are highly significant differences in the time expected to achieve delivery in the four groups (log rank χ^2 (3 df) = 9932): whereas 80% of multiparae without an epidural are delivered within half an hour, nulliparae with epidurals would not achieve this cumulative delivery rate until they had been in the second stage for 7 h.

Maternal age, birthweight and maternal height were included in a stepwise analysis as covariables. Maternal age and birthweight were strongly positively associated with time to delivery (incremental log rank χ^2 (1 df) = 242·9 and 166·5 respectively, $P<0{\cdot}0001$). Maternal height was also associated (incremental log rank χ^2 (1 df) = 40·3, $P<0{\cdot}0001$).

Table 4. Intraregional variations in second stage management and outcomes

	Range (%)
Epidural rate	1·8 to 29·9
Use of oxytocin augmentation	7·3 to 29·3
Overall forceps rate	7·0 to 14·2
LSCS in second stage	0·1 to 1·5

LSCS = Lower segment caesarean section.

Table 4 shows the range of values for second stage characteristics in the 17 individual obstetric units contributing to the database. A significant correlation was found between the epidural rate in each unit and the overall forceps rate in the same unit (r = 0·61, $P<0{\cdot}01$). There was no significant correlation between the rate of oxytocin augmentation in each unit and the forceps rate, nor between oxytocin augmentation and the rate of caesarean section in the second stage. There was, however, a significant correlation between the unit epidural rate and the frequency of caesarean section in the second stage of labour (r = 0·53, $P<0{\cdot}05$).

Discussion

This study records the characteristics of second stage labour in 25 069 women delivered within a 12 month period in one Regional Health Authority. It is not possible to determine accurately the time at which full dilatation of the cervix was reached, but any error would tend to underestimate the duration of the second stage of labour. In previous publications this duration has usually been recorded in terms of mean values although it is not a normally distributed variable and censoring occurs at the time of operative delivery. In women who did not receive epidural analgesia the mean durations of the second stage in our Health Region are remarkably similar to those quoted by Friedman (1955 and 1956) over 30 years ago, but greater than the values from other studies where the analysis has been confined to women who gave birth spontaneously (Duignan *et al.* 1975; Kilpatrick & Laros 1989).

The effect of epidural analgesia on the duration of the second stage and the rate of instrumental delivery is well known (Hoult *et al* 1977; Studd *et al.* 1980). In our study the mean duration of the second stage in women using epidural analgesia is longer than originally quoted by Studd *et al* (1980) and probably reflects a more conservative approach to the management of such women in an attempt to improve the rate of spontaneous delivery (Maresh *et al* 1983; Reynolds & Yudkin 1987).

It is generally recognized that a greater proportion of high risk women, such as those with dysfunctional labour or fetal malposition, will be offered epidural analgesia and that the effect of selection bias contributes to the less favourable outcomes. In our population small but significant differences in maternal age and infant birthweight were seen between women who received epidural analgesia and those who did not.

Our data clearly demonstrate the differing durations of the second stage of labour in women of differing parity, with or without epidurals. However, it is interesting that the duration of the second stage in parous women using epidural analgesia is similar to that of nulliparae without epidurals, and operative intervention is more likely in parous women who have epidurals than in nulliparae who do not. Knowledge of this might influence the decision of a parous women whether or not to use epidural analgesia.

It appears from Fig. 1 that there is little to be gained from waiting longer than 1 h for spontaneous delivery in a parous woman without an epidural. The appropriate time for intervention is less clearly defined in the other three groups, who continue to give birth at a steady rate for several more hours.

One of the advantages of a database collected routinely is that it records current practice: not necessarily the best that can be achieved but what happens in reality. Comparison of data from 17 different maternity units also allows the effect of differing practices on the duration of the second stage to be examined. In individual obstetric units, correlations were found between the rate of epidural use and both the length of the second stage and the overall forceps rate in that unit. These findings are not unexpected but have not been reported before.

Perhaps more surprising is the apparent relation between the epidural rate in each unit and the occurrence of caesarean section in the second stage. It may be that epidural analgesia, by interfering with normal second stage mechanisms responsible for descent and rotation of the vertex, contributes to caesarean section as well as forceps rates. This possibility has been raised previously (Thorp *et al.* 1989) but the question could only be resolved by prospective controlled studies of appropriate size. The correlations mentioned above need further study as they have been carried out on groups rather than individual women.

This study illustrates the heterogeneity of an obstetric population. In 1988 in North West Thames the time required to deliver 80% of a defined group of women varied by a factor of 14 depending on their parity and the method of analgesia employed. This needs to be taken into consideration when second stage management policies are being defined. As the risks of maternal or fetal morbidity do not increase unduly with the duration of the second stage (Saunders *et al* 1992), the timing of intervention should be influenced by the condition of the mother and fetus rather than the elapsed time from full dilatation of the cervix.

Acknowledgments

We would like to thank Professor Beard, who established the data collection system, for his advice, the consultants in participating hospitals for their continuing support, and the midwives who enter the data, without whom such analyses would not be possible.

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Received 8 April 1991
Accepted 20 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 381–385

OBSTETRICS

Neonatal and maternal morbidity in relation to the length of the second stage of labour

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ABSTRACT

Objective To investigate the relation between the duration of the second stage of labour and subsequent early neonatal and maternal morbidity.

Design Retrospective analysis of a regional obstetric database.

Setting 17 maternity units in the North West Thames Health Region.

Subjects Selected from 36 727 consecutive singleton deliveries in 1988. The analysis was confined to the 25 069 women delivered of an infant of at least 37 weeks gestation with a cephalic presentation following the spontaneous onset of labour.

Main outcome measures The relative risk of early maternal morbidity, postpartum haemorrhage (PPH) and postpartum infection, and neonatal morbidity, as judged by low Apgar scores or admission to the special care baby unit (SCBU), in relation to anthropomorphic characteristics (parity and birthweight), interventions (epidural analgesia, episiotomy and operative delivery), signs of fetal compromise (meconium staining of the amniotic fluid or abnormal cardiotocography (CTG)), maternal morbidity in labour (pyrexia) and the duration of the second stage of labour.

Results The duration of the second stage of labour had a significant independent association with the risk of both PPH and maternal infection after adjustment for other factors. However, there was a similar or greater risk of PPH in association with operative delivery or a birthweight greater than 4000 g. Both maternal pyrexia in labour and primiparity were associated with a greater risk of post partum maternal infection than was the duration of the second stage, although all these factors were statistically significant. In contrast, the duration of the second stage was not significantly associated with the risk of a low Apgar score or admission to SCBU after adjustment for other factors.

Conclusions The duration of the second stage of labour has a positive independent association with early maternal morbidity. We could show no such relation between time spent in the second stage of labour and the frequency of low Apgar scores or the rate of admission to SCBU. With current management approaches, in the absence of factors suggesting fetal compromise, second stage labours of up to 3 h duration do not seem to carry undue risk to the fetus.

The second stage of labour begins at full dilatation of the cervix and ends with the birth of the fetus. The ideal management of the second stage should allow the greatest chance of spontaneous delivery with the least risk of maternal morbidity and infant morbidity and mortality. There is, however, a lack of consensus regarding the optimum management of the second stage, particularly with respect to its duration. Arbitrary time limits have been (and still are) applied to the second stage leading to operative intervention in many cases even in the absence of any evidence of maternal or fetal compromise. This approach is based on the concept that for labour to exceed these arbitrary time limits is hazardous to the mother and baby. To assess the validity of this concept the second stage characteristics of 25 069 women who were delivered within the North West Thames Health Region in 1988 were related to maternal and fetal morbidity.

Subjects and methods

In order to study a relatively homogeneous population the analysis was confined to the 25 069 women who were delivered of a singleton fetus of at least 37 weeks gestation with a cephalic presentation after labour of spontaneous onset, who were the subject of our previous report (Paterson *et al.* 1992). A low Apgar score was a score of <7 at 5 min. Postpartum infection included proven wound, endometrial and urinary tract infection, or the presence of a pyrexia of unknown origin >38°C on two separate occasions.

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Table 1. Duration of the second stage by parity and use of epidural analgesia

	Duration of second stage (min)							
	Epidural				No epidural			
Parity	*n*	Mean (SD)	Median	(IQ range)	*n*	Mean (SD)	Median	(IQ range)
0	2662	97 (68)	82	(45–134)	8270	58 (46)	45	(27–76)
≥1	978	54 (55)	33	(17–70)	13159	19 (21)	13	(8–22)

IQ range = interquartile range.

Statistical analysis

The 95% confidence intervals (CI) for differences in mean values, and proportions, and unadjusted odds ratios were calculated using CIA software (Gardner *et al.* 1989). All other analyses were performed using SAS (SAS Institute Inc. 1985). Logistic regression analysis was used to model the relation between maternal and fetal morbidity including postpartum haemorrhage (PPH), postpartum infection, low Apgar scores and admission to the special care baby unit (SCBU) and factors that were associated with such morbidity. Variables considered risk factors for maternal and fetal morbidity were parity, epidural analgesia administered in the first stage of labour, maternal pyrexia in labour (>38°C), abnormal fetal heart rate patterns, meconium staining of amniotic fluid, duration of the second stage, operative delivery, episiotomy and fetal birthweight. Initially all these variables were entered into each model, but only those with a significance of $P<0{\cdot}01$ were retained, together with the duration of the second stage, for the final analysis. The results are presented as odds ratios for all variables and adjusted odds ratios (approximations for relative risk) for variables entered into the final model; 95% CI are shown for all odds ratios.

Results

Of the total of 25 069 women who satisfied the selection criteria for this study 10 932 were nulliparae and 14 137 were parous. Epidural analgesia had been employed in 24% of nulliparae and 7% of the parous women. Mean and median values for the duration of the second stage are given in Table 1.

When maternal morbidity was related to the duration of the second stage there was an increased risk of PPH and febrile morbidity with time, but this effect was much less apparent in women who gave birth spontaneously (Figs 1 and 2). Logistic regression analysis indicated that the duration of the second stage of labour had a significant independent association with both PPH and postpartum infection. However, the principal associations with PPH were operative delivery (adjusted odds ratio 2·9) and a fetal birthweight ≥ 4000 g (adjusted odds ratio 2·7). The use of epidural analgesia and a fetal birthweight between 3500 and 3999 g were also associated with an increased risk (adjusted odds ratios 1·4 and 1·5 respectively) (Table 2). Maternal postpartum infection was strongly associated with maternal pyrexia in labour (adjusted odds ratio 6·0) and primiparity (adjusted odds ratio 2·5) (Table 2). There was no significant increase in the risk of infection in association with the duration of the second stage until 4 h had elapsed when the risk doubled.

In contrast, the duration of the second stage was not significantly associated with the risk of a low Apgar score or admission to SCBU. The risk of both these outcomes was increased in association with antepartum indicators which might suggest fetal compromise: maternal pyrexia and meconium staining of the amniotic fluid. The strongest association

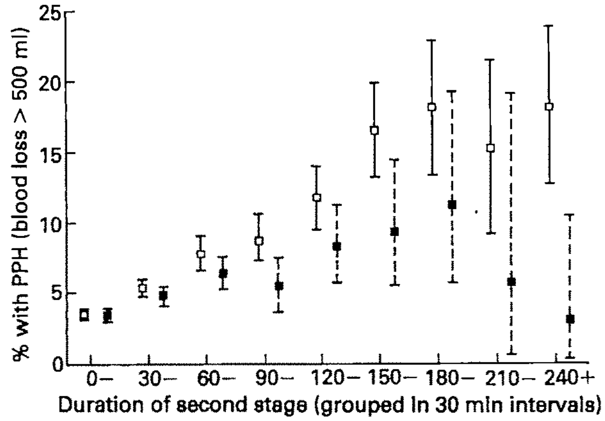

Fig. 1. The proportion of women with a postpartum haemorrhage (PPH), blood loss >500 ml, in relation to the duration of the second stage of labour (with 95% CI). The open squares show the rates for all deliveries and the solid squares the rates for spontaneous deliveries only.

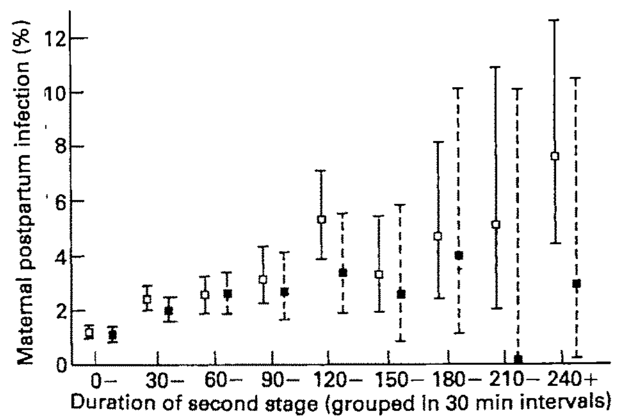

Fig. 2. The proportion of women with post partum infection in relation to the duration of the second stage of labour (with 95% CI) The open squares show the rates for all deliveries and the solid squares the rates for spontaneous deliveries only.

Table 2. The proportions of women with postpartum haemorrhage (PPH) (blood loss ⩾ 500 ml) and those with postpartum infection showing the crude and adjusted odds ratios*

	Number	Number (%) with PPH	Odds ratios (95% CI)	Adjusted odds ratios (95% CI)	Number (%) with Infection	Odds ratios (95% CI)	Adjusted odds ratios (95% CI)
Parity							
Primiparae	10932	801 (7)	1·8 (1·6 to 2·1)		359 (3)	3·2 (2·6 to 3·9)	2·5 (2·0 to 3·0)
Multiparae	14137	584 (4)			149 (1)		
Epidural analgesia							
Yes	3640	374 (10)	2·1 (1·9 to 2·4)	1·4 (1·2 to 1·6)	154 (4)	2·6 (2·2 to 3·2)	
No	21429	1101 (5)			354 (2)		
Maternal pyrexia in labour							
Yes	193	26 (13)	2·7 (1·8 to 4·1)		32 (17)	10·2 (6·9 to 15·0)	6·0 (4·0 to 9·0)
No	24876	1359 (5)			476 (2)		
Meconium stained amniotic fluid							
Yes	3871	286 (7)	1·5 (1 3 to 1·7)		109 (3)	1·8 (1·4 to 2·2)	
No	21198	1099 (5)			399 (2)		
Abnormal cardiotocography							
Yes	3959	327 (8)	1·7 (1·5 to 1·9)		143 (4)	2·1 (1·8 to 2·6)	
No	21110	1058 (5)			365 (2)		
Second stage duration (min):							
<120	23183	1105 (5)			413 (2)		
120–179	1313	179 (14)	3·2 (2·7 to 3·7)	1·6 (1·3 to 1 9)	61 (5)	2·7 (2·0 to 3·5)	1·2 (0·9 to 1·7)
180–239	382	66 (17)	4·2 (3·2 to 5·5)	1·7 (1·3 to 2·3)	19 (5)	2·9 (1·8 to 4·6)	1·2 (0·8 to 2·1)
⩾240	191	35 (18)	4·5 (3·1 to 6·5)	1·9 (1·2 to 2·8)	15 (8)	4·7 (2·8 to 8·0)	2·1 (1·2 to 3·7)
Operative delivery							
Yes	2648	417 (16)	4·1 (3·7 to 4·7)	2·9 (2·5 to 3·4)	145 (6)	3·5 (2·9 to 3·2)	2 0 (1·6 to 2·5)
No	22421	986 (4)			363 (2)		
Episiotomy							
Yes	7341	657 (9)	2·3 (2·1 to 2·6)		217 (3)	1·8 (1·5 to 2·2)	
No	17728	728 (4)			291 (2)		
Birthweight (g)							
<2500	506	13 (3)	0·6 (0·3 to 1·0)	0·6 (0·4 to 1·1)	15 (3)	1·5 (0·9 to 2·6)	
2500–3499	14826	629 (4)			290 (2)		
3500–3999	7425	487 (7)	1·6 (1 4 to 1·8)	1·5 (1 3 to 1·7)	148 (2)	1·0 (0·8 to 1·3)	
⩾4000	2312	256 (11)	2·8 (2 4 to 3·3)	2·7 (2·3 to 3·1)	55 (2)	1·2 (0·9 to 1·6)	

*The adjusted odds ratios for PPH are presented in relation to reference categories of women who laboured without epidural analgesia, a second stage duration <120 min spontaneous vaginal delivery and an infant weighing 2500–3499 g; for postpartum infection the reference categories are multiparous women, no pyrexia in labour, a second stage duration <120 min and a spontaneous vaginal delivery.

with admission to SCBU was a fetal birthweight <2500 g (adjusted odds ratio 5·9), followed by maternal pyrexia (adjusted odds ratio 3·9) and meconium-stained amniotic fluid (adjusted odds ratio 2·1) (Table 3). Operative delivery was associated with a doubling of risk and an abnormal CTG with a 50% increase in adjusted risk. Babies weighing ⩾4000 g were also more likely to be admitted to SCBU (adjusted odds ratio 1·3).

A low 5-min Apgar score was associated with meconium staining of the amniotic fluid (adjusted odds ratio 2·7) and an abnormal CTG (adjusted odds ratio 2·1) (Table 3).

It is not possible to comment on the influence of the duration of the second stage on perinatal mortality (Fig. 3) since the confidence intervals widen beyond 150 min because of the small number of women undelivered after this time.

Discussion

Prolonged labour has always been viewed as potentially hazardous. The diagnosis of a prolonged second stage is, however, based purely on arbitrary criteria.

In an attempt to prevent unnecessary and potentially dangerous meddling, Denman (1817), an eminent 19th century obstetrician, recommended a 6 h second stage before the use of forceps was even contemplated. Harper (1859) published retrospective data which suggested that more active intervention was associated with improved fetal and maternal outcome, although the mean duration of the second stage was not recorded. It is interesting that Harper was opposed to the use of time limits in labour but suggested that progress should be the sole criterion for management policy. In this century, De Lee (1920) advocated prophylactic episiotomy and forceps delivery in the belief that this would reduce trauma to the pelvic floor and the fetal brain although no evidence was presented to support this approach.

Hellman & Prystowsky (1952) reported an increase in infant mortality, postpartum haemorrhage and puerperal febrile morbidity in second stage labours >2 h duration. The British Perinatal Mortality Survey of 1958 (Butler & Bonham 1963) was interpreted as showing an increase in perinatal mortality in second stage labours >2 h duration and these concerns were supported by evidence of progressive fetal acidaemia in the second stage (Pearson & Davies 1974).

Table 3. The proportions of infants admitted to the special care baby unit (SCBU) and those with low 5-min Apgar scores showing the crude and adjusted odds ratios*

	Number	Number (%) admitted to SCBU	Odds ratios (95% CI)	Adjusted odds ratios (95% CI)	Number (%) Apgar score @ 5 min <7	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Parity							
Primiparae	10932	670 (6)	1·7 (1·5 to 1·9)		147 (1)	1·3 (1·0 to 1·7)	
Multiparae	14137	538 (4)			145 (1)		
Epidural analgesia							
Yes	3640	231 (6)	1·4 (1·2 to 1·6)		58 (2)	1·5 (1·1 to 2·0)	
No	21429	977 (5)			234 (2)		
Maternal pyrexia in labour							
Yes	193	42 (22)	5·7 (4·0 to 8·0)	3·9 (2·6 to 5·4)	7 (4)	3·3 (1 5 to 7·0)	
No	24876	1166 (5)			285 (1)		
Meconium stained amniotic fluid							
Yes	3871	352 (9)	2·4 (2·1 to 2·7)	2·1 (1·8 to 2·3)	107 (3)	3·2 (2 5 to 4·1)	2·8 (2·2 to 3·6)
No	21198	856 (4)			185 (1)		
Abnormal cardiotocography							
Yes	3959	343 (9)	2·2 (2·0 to 2·5)	1·5 (1·3 to 1 7)	96 (2)	2 7 (2·1 to 3·4)	2·1 (1 7 to 2·8)
No	21110	365 (2)			196 (1)		
Second stage duration (min)							
<120	23183	1064 (5)			261 (1)		
120–179	1313	100 (8)	1·7 (1 4 to 2·1)	1 1 (0·9 to 1·4)	22 (2)	1·5 (0·97 to 2·3)	1·3 (0·8 to 2·0)
180–239	382	20 (7)	1·6 (1·1 to 2·4)	1 1 (0·7 to 1·6)	4 (1)	0·9 (0·3 to 2·5)	0·9 (0·3 to 2·3)
≥240	191	16 (8)	1·9 (1·1 to 3·2)	1 2 (0·7 to 2·0)	5 (3)	2·4 (0·96 to 5·8)	1·9 0·8 to 4·7)
Operative delivery:							
Yes	2648	277 (11)	2·7 (2·3 to 3·1)	2·0 (1·7 to 2 4)	55 (2)	2·0 (1·5 to 2·7)	
No	22421	931 (4)			237 (1)		
Episiotomy:							
Yes	7341	485 (7)	1·7 (1 5 to 1·9)		103 (1)	1·3 (1·0 to 1·7)	
No	17728	723 (4)			189 (1)		
Birthweight (g)							
<2500	506	115 (23)	6·3 (5·1 to 7·9)	5 9 (4·7 to 7·4)	17 (4)	3·1 (1·9 to 5·2)	
2500–3499	14826	659 (4)			164 (1)		
3500–3999	7425	292 (4)	0·9 (0·8 to 1·0)	1 2 (1·0 to 1·3)	72 (1)	0 9 (0·6 to 1·1)	
≥4000	2312	142 (6)	1·4 (1·2 to 1·7)	1·3 (1·1 to 1·6)	39 (2)	1·5 (1·1 to 2·2)	

*The adjusted odds ratios for admission to SCBU are presented in relation to reference categories of women with no pyrexia in labour, no meconium in amniotic fluid, a normal CTG, a second stage duration <120 min, a spontaneous vaginal delivery and an infant weighing 2500 to 3499 g, for low Apgar scores the reference categories are a normal CTG and a second stage duration <120 min.

During the past 10–15 years, however, there has been a reassessment of the risks of second stage labour. Cohen (1977) studied over 4000 women and reported no increase in perinatal mortality or low Apgar scores in those with second stage labours lasting up to 3 h, provided that fetal monitoring was undertaken. In women using epidural analgesia delay in the start of maternal pushing does not appear to affect adversely fetal pH at delivery (Maresh *et al.* 1983) and, if the supine position is avoided, progressive fetal acidosis can be prevented (Johnstone *et al.* 1987).

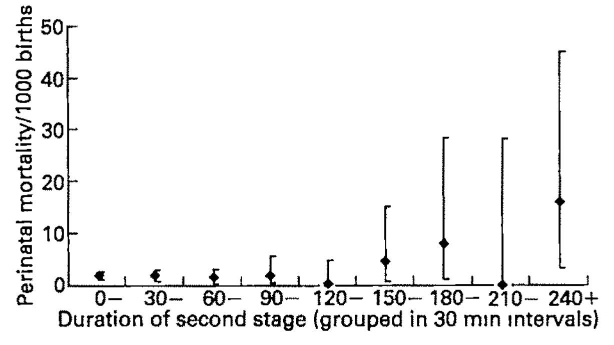

Fig. 3. Perinatal mortality rates in relation to the duration of the second stage of labour (with 95% confidence intervals).

Our study, which represents one of the largest analyses of second stage labour yet undertaken, supports these more recent conclusions. After adjustment for confounding factors our data show no convincing relation between infant mortality and morbidity and duration of the second stage <3 h.

In addition, although the frequency of maternal morbidity (postpartum haemorrhage and infection) appears to rise with increasing duration of the second stage, this effect is much less marked in women who give birth spontaneously. Cohen (1977) concluded that the increase in morbidity with time was entirely due to the greater use of midforceps delivery in prolonged labours. However, our larger study indicates that although operative delivery is associated with a significantly increased risk of maternal morbidity, other factors such as parity, pyrexia in labour, fetal birthweight and the duration of the second stage itself are all independently associated with maternal morbidity. The duration of active maternal pushing is not recorded on the database. This component of the second stage may prove to be more important than the total length of the second stage of labour. However, there is evidence to suggest that the duration of the active phase of the second stage is relatively constant irrespective of when pushing actually begins (Maresh 1983).

Whether second stage duration influences long term maternal morbidity such as genital prolapse and urinary incontinence has yet to be determined. Evidence that pelvic floor denervation is more likely with a long second stage (Allen *et al.* 1990) is difficult to interpret because of confounding variables such as birthweight.

Poor fetal outcome is associated with known indicators of fetal compromise but, after adjustment for these, second stages of up to 3 h do not seem to carry undue risk to the fetus in our Region. Women allowed to remain in the second stage of labour for this length of time may, however, suffer a higher rate of early morbidity. This modest increase in risk might be considered acceptable if a larger proportion of women are able to give birth spontaneously as a result.

Acknowledgments

We would like to thank Professor Beard, who established the data collection system, for his advice, the consultants in participating hospitals for their continuing support, Andy Dawson and the maternity team at the Regional Computer Centre and the midwives who enter the data, without whom such analyses would not be possible.

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Received 8 April 1991
Accepted 20 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 386–391

FETAL AND NEONATAL MEDICINE

Falling incidence of hypoxic-ischaemic encephalopathy in term infants

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ABSTRACT

Objective To examine trends in the incidence of hypoxic-ischaemic encephalopathy over a 13-year period.

Design A retrospective analysis of medical records of all infants admitted in the years 1976–1980 and 1984–1988.

Setting A large non-teaching district health authority in central England.

Subjects Infants admitted to a district general hospital neonatal unit with clinical features of hypoxic-ischaemic encephalopathy.

Main outcome measures Incidence of three grades of hypoxic-ischaemic encephalopathy, handicap and mortality.

Results During the first 5-year period the overall incidence of hypoxic-ischaemic encephalopathy was 7·7 per 1000 live births with 2·6 per 1000 live births being severely affected (grades II and III). In the second 5-year period the overall incidence was 4·6 per 1000 live births with 1·8 per 1000 live births being severely affected. The difference in the overall rate is statistically significant. Of the infants with severe encephalopathy 61% had Apgar scores below 4 at 1 min and 60% were born by instrumental or operative delivery.

Conclusions The fall in incidence of hypoxic-ischaemic encephalopathy has occurred during a period of falling perinatal mortality rate. It was instructive to find that infants born vaginally and without obstetric intervention formed a larger fraction of the severely affected infants in the later period.

The incidence of hypoxic-ischaemic encephalopathy has been suggested as a useful indicator of quality of care (Dennis & Chalmers 1982) and its severity has been shown to be a useful predictor of outcome (Levene *et al.* 1986). The admission of three infants with severe hypoxic-ischaemic encephalopathy within the space of 3 weeks into a neonatal unit serving a population of around 5000 births per year led to this study. The aim was to determine whether or not there had been a recent increase in the incidence of hypoxic-ischaemic encephalopathy and, if so, whether there were practices which needed review.

Subjects and methods

The infants

The medical records of all infants over 37 weeks gestation and admitted to the City neonatal unit in two 5-year periods, 1976 to 1980 and 1984 to 1988 were studied. For practical reasons, constrained by time and resources, it was decided to study data from a total of 10 years. As complete data were available from 1976–1988, a 3-year gap between the study periods was chosen to achieve the longest possible time span for the study, and to cover a period during which the intensity of fetal monitoring in labour had increased. Those records where the infant was described as having the features of hypoxic-ischaemic encephalopathy were identified.

The illness was graded according to the following criteria used by Levene *et al.* (1985). Grade I (mild): irritability, 'hyperalert' mild hypotonia, poor sucking. Grade II (moderate): lethargic, seizures, marked abnormalities of tone, required tube feeding. Grade III (severe): comatose, prolonged seizures, severe hypotonia, failure to maintain spontaneous respiration.

An element of judgement enters into this classification because not all features of each category were present in every infant. A progression of symptoms over the first 48 h with complete clinical recovery by 5 days was required for grade I; seizures, marked abnormalities in tone and poor feeding were required for grade II; and many seizures and ventilatory support for grade III.

Infants with hypoglycaemia and irritability were included if the neurological abnormalities persisted after the blood glucose had been corrected.

Outcome

The records also contained information on the infants' pro-

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gress. Some infants died. All those with grades II and III encephalopathy were followed up in clinic, the majority were discharged if their progress was judged to be satisfactory by 18 months of age. All those who were recorded to have a severe motor disability at 18 months, such as spastic quadriplegia, hemiplegia or diplegia were included in this analysis. Others noted to have less precise problems such as delayed development or speech problems were not included.

Information

A proforma was completed for each infant identified. The following information was sought: maternal age and parity, length of first and second stage of labour, mode of delivery, indications for any assisted delivery, presence of meconium staining of amniotic fluid, birthweight, head circumference, sex, Apgar scores at 1 and 5 min and whether or not the infants were intubated and artificially ventilated during resuscitation. The records were usually complete for all these items. Initially the notes were also searched for evidence of fetal distress, and for blood gas estimates after birth but the data were incomplete and occasionally unclear and therefore not helpful for the purposes of this enquiry.

Population

The City Hospital neonatal unit serves the adjacent maternity unit and several smaller maternity homes in a large district health authority whose population of around 450 000 is centred on a city with a population of 220 000. The population is stable, with a small cross boundary flow of less than 20% to a neighbouring health authority. The number of babies born in these units has changed since 1976, with an increasing proportion of infants being born at the City Hospital maternity unit. The relevant birth rates in each unit are shown in Fig. 1. There is no other neonatal unit in the area and presumably all infants who developed grades II and III encephalopathy, and probably the majority with grade I, would have been transferred to the unit.

A wider population enquiry was not made so the possibility that some very ill infants were transferred to units outside the city, or that the occasional infant was transferred in from elsewhere cannot be excluded. Movement in either direction, if any, is likely to have been very small. Admission policies, transfer policies and their rates have not changed significantly during the period and the calculations of incidence were based on the assumption that these were negligible.

Statistics

All statistical analyses used the χ^2 test for fourfold tables.

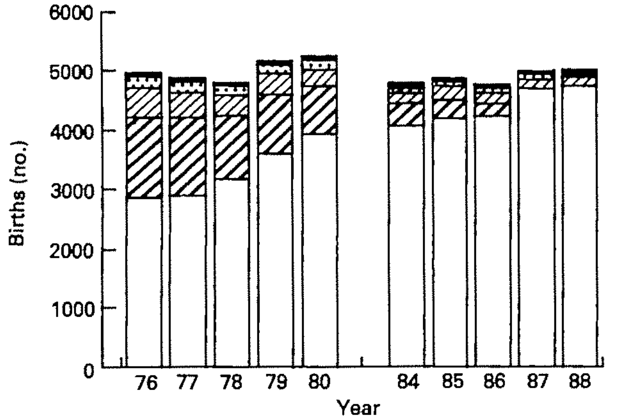


Fig. 1. Distribution of place of delivery in the city area in the two 5-year groups. (■) Home, (▨) District Maternity Hospital A, (▨) District Maternity Hospital B, (▨) Maternity homes, (□) City Hospital.

No. of births per year

Year	City hospital	Mat. homes	Hospital 'B'	Hospital 'A'	Home
1976	2881	1300	513	187	50
1977	2901	1293	416	188	48
1978	3171	1052	331	163	55
1979	3581	972	352	148	53
1980	3928	777	296	135	34
1984	4077	334	195	92	47
1985	4167	337	200	80	60
1986	4203	197	196	73	54
1987	4689	0	158	65	61
1988	4736	0	130	63	51

Results

Incidence

During the first 5-year period (1976–1980) there were 24 824 births in the maternity services served by the neonatal unit. There were 280 stillbirths (11·3 per 1000 births). From the medical notes of infants admitted to the unit, 189 infants were recorded as having features of hypoxic-ischaemic encephalopathy; 126 grade I, 39 grade II and 24 grade III. Thus the overall incidence was 7·7 per 1000 live births, and the rate for the severely affected infants (grades II and III) was 2·6 per 1000 live births (Fig. 2). During the second 5-year period (1984–1988) there were 24 265 births and by 1988 the great majority were in the adjacent maternity unit. There were 138 stillbirths (5·7 per 1000 births). From the notes examined in

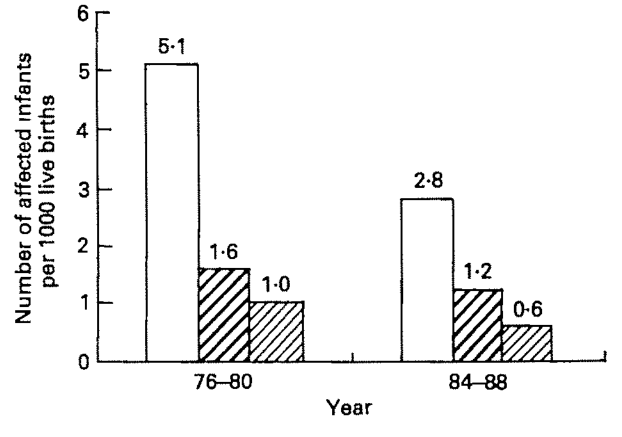


Fig. 2. Incidence of hypoxic-ischaemic encephalopathy according to grade. (□) grade I, (▨) grade II, (▨) grade III.

this period, 112 contained reports of hypoxic-ischaemic encephalopathy; 68 grade I , 29 grade II and 15 grade III.

Thus the overall incidence was around 4·6 per 1000 live-births, with the rate of severely affected infants (grades II and III) of 1·8 per 1000 live births. The difference in overall rates was statistically significant ($P<0{\cdot}001$). Although the number of severely affected infants was less in the second period, the numbers are small and the difference is not statistically significant.

Maternal factors

Table 1 gives the percentage of the mothers of the infants who developed severe encephalopathy (grades II and III) who were under 20 years, over 35 years, primigravid, or whose pregnancy was estimated to have continued for over 41 completed weeks. The findings are compared with the Cardiff Births Survey (Andrews *et al.* 1986). The percentages quoted are taken from an article by Minchom *et al.* (1987) and are based on 41 090 live born singleton infants born at or after term in the Cardiff area during 1970–1979 and who had not experienced early-onset seizures. With respect to age and gestation the mothers of grade I infants in Derby were similar to those in the Cardiff area. A statistically significantly higher proportion of mothers whose infants developed grades II or III encephalopathy were <20 years of age, had a gestational length of >41 weeks and were primigravid compared with the Cardiff data. Table 1 also shows the often reported but poorly understood phenomenon that male infants are more likely to suffer hypoxic-ischaemic encephalopathy compared with female infants.

Delivery

Table 1 shows the percentages with over 15 h in the first stage of labour and over 2 h in the second stage of labour, the mode of delivery and whether meconium staining was recorded. The infants who developed hypoxic-ischaemic encephalopathy had head circumferences within the normal range (data not shown).

Overall 5% of infants with grade I encephalopathy were born after a long second stage, 64% had some form of assisted delivery. Compared with grade I, a lower percentage of infants with grades II and III encephalopathy were born by forceps/ventouse and caesarean section taken together. The forceps/ventouse and section rates for all infants with encephalopathy was lower in the second than in the first 5-year period. Fetal distress was given as the indication for assisted vaginal delivery in 41 of 67 (61%) births, and 32 of 57 (56%) births by caesarean section in the grade I group and for grades II and III combined it was 18 of 26 (69%), and 34 of 38 (89%) respectively.

The rates of assisted vaginal deliveries and caesarean sections performed in the main maternity unit between 1977 and 1980 were 20·6% and 7·6% respectively. If it is assumed that the number of forceps deliveries in the smaller maternity homes is negligible this gives an assisted delivery rate of 14·0% of all deliveries in this time period. In the period 1984–1988 the section rate was 11·1% and the rate of assisted vaginal delivery 15·2% of the deliveries within the maternity unit and 13·7% of all deliveries in that time period.

Resuscitation

Table 1 gives the percentage of infants with Apgar scores 0–3

Table 1. Characteristics of mothers, labour and birth details associated with 107 infants with severe encephalopathy (grades II and III) born during two 5-year study periods, 1976–1980 and 1984–1988 compared with 41 090 normal infants from the Cardiff Birth Survey*

	Severe encephalopathy during study period.								
	1974–1980 (*n* = 63)		1984–1988 (*n* = 44)		Both periods (*n* = 107)		Cardiff data* (*n* = 41 090)	Significance†	
	n	(%)	*n*	(%)	*n*	(%)	(%)	χ^2	*P*
Maternal age (years)									
<20	12	(19)	11	(25)	23	(21)	13 9	5·14	<0·025
>35	6	(10)	4	(9)	10	(9)	5·8	2·45	>0·05
Primigravid	29	(46)	25	(57)	54	(50)	40·6	4·31	<0·05
Gestation >41 weeks	24	(38)	21	(48)	45	(42)	25·4	15·61	<0·001
Male infant	41	(65)	29	(66)	70	(65)	51·1	8·76	<0·01
Duration of labour									
Stage 1 >15 h	7	(11)	6	(14)	13	(12)	11 2	0·10	>0·05
Stage 2 >2 h	0		2	(5)	2	(2)	0 8	1·54	>0·05
Mode of delivery									
Unassisted	23	(37)	20	(45)	43	(40)	7·9	96·71	<0·001
Forceps/Ventouse	17	(27)	9	(20)	26	(24)	16·7	4 45	<0·05
Caesarean section	23	(37)	15	(34)	38	(36)	4·3	248·0	<0·001
Meconium	18	(29)	23	(52)	41	(38)	–	–	–
Low Apgar scores									
0–3 at 1 min	42	(67)	23	(52)	65	(61)	3·1	1127	<0·001
0–5 at 5 min	36	(57)	16	(36)	52	(48)	–	–	–
Birthweight (kg)									
<2·5	12	(19)	5	(11)	17	(16)	4·1	37·47	<0·001
>4 0	5	(8)	4	(9)	9	(8)	8·3	0·00	>0·05

*Data derived from Minchom *et al* (1987) and Andrews *et al* (1986).

†Significance of difference between Cardiff data and severe encephalopathy during total 10-year study period

at 1 min and 0–5 at 5 min and the percentage of infants with birthweights either under 2·5 kg or over 4·0 kg. Over 40% of all infants had a depressed response at birth, and over 20% were still in trouble at 5 min. Looked at another way, however, in the 1984–1988 period, 64% of infants who developed grades II and III encephalopathy had Apgar scores >5 at 5 min. Table 2 shows the Apgar scores of the 107 infants who subsequently developed grades II and III encephalopathy according to their mode of birth. Nineteen of the 26 with grade II encephalopathy and 6 of the 17 with grade III encephalopathy, who were the result of spontaneous vaginal deliveries, had Apgar scores >5 at 5 min. Of the 25 infants with Apgar scores >5 at 5 min, 19 had Apgar scores >3 at 1 min.

Small infants (less than 2·5 kg) were over represented, large infants were not.

Outcomes

These are shown in Table 3 and Fig. 3. In the first 5-year period (1976–1980) 22 of 24 infants with grade III encephalopathy died and both survivors are now severely disabled. The mean time to onset of first seizure was 8·5 h and the mean age at death was 46·5 h. In the 1984–1988 period, 12 of 15 infants died but two of the survivors were reported to be normal at follow-up, the other has spastic quadriplegia and epilepsy. The mean time to onset of first seizure was 8 h and the mean age at death was 58 h.

In the follow-up records for infants with grade I encephalopathy there was no indication of any infant with severe motor disability. Thirty-nine infants had grade II encephalopathy in the years 1976–1980. The mean time to onset of first seizure was 23 h. Of these 39 infants, six have spastic quadriplegia, one diplegia and two have mild spastic hemiplegia. Twenty-nine infants had grade II encephalopathy in the years 1984–1988. The mean time of onset of first seizure was 16 h. Of these 29 infants, four have spastic quadriplegia and one has a mild spastic hemiplegia.

Of the 43 infants with grades II and III encephalopathy who were the result of spontaneous vaginal delivery, 25 had Apgar scores >5 at 5 min. The disabilities which these infants were to develop were not revealed by their response to birth. Of the 25 infants in this group with good Apgar scores, 4 of the 19 with grade II encephalopathy developed motor disabilities subsequently and 4 of the 6 with grade III encephalopathy died. Of the two survivors one developed spastic quadriplegia and the other was normal at follow-up.

Discussion

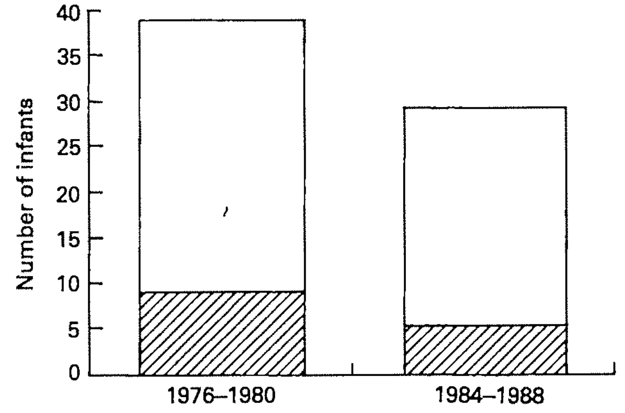
This study has shown a significant fall in incidence of hypoxic-ischaemic encephalopathy between the two 5-year periods, 1976–1980 and 1984–1988. The fall in incidence of hypoxic-ischaemic encephalopathy should be considered against the background of falling stillbirth and perinatal mortality rates over this period. Many factors could account for this, including obstetric practice, organization of services and demographic changes in the child-bearing population.

Many attempts have been made to identify infants at risk of suffering asphyxial brain damage. Over the last 10 years fetal cardiotocography and scalp blood sampling has been widely introduced into obstetric practice. In the City Hospital in 1976 there were two fetal cardiotocograph recorders and in 1988 there were 14. The maternity unit acquired a blood gas analyser to measure scalp blood gases in 1980. Thus during the first study period fetal heart monitoring was not widely used, in the

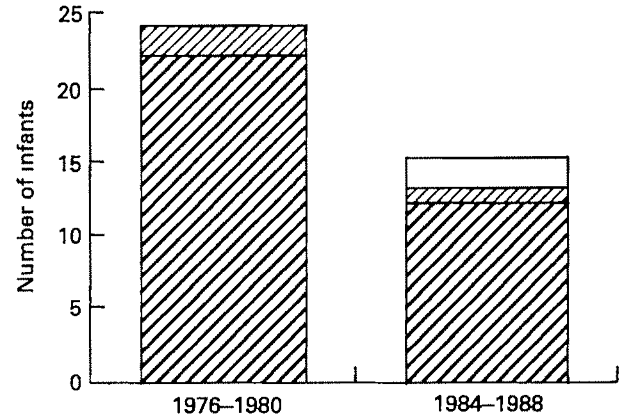
Table 2. Low Apgar scores according to mode of birth for 107 infants who developed grades II and III encephalopathy

	Normal vaginal delivery (*n* = 43)		Assisted delivery (*n* = 26)		Caesarean section (*n* = 38)	
Apgar score	*n*	(%)	*n*	(%)	*n*	(%)
0–3 at 1 min	20	(47)	17	(65)	28	(74)
0–5 at 5 min	18	(42)	14	(54)	20	(53)

Results are numbers of infants with percentage in parenthesis.



Grade II encephalopathy



Grade III encephalopathy

Fig. 3. Outcome of infants with grades II and III encephalopathy in two 5-year periods, 1976–1980 and 1984–1988. (□) normal, (▨) abnormal, (▩) death.

	Grade II encephalopathy		Grade III encephalopathy	
Outcome	1976–1980	1984–1988	1976–1980	1984–1988
Normal	30	24	0	2
Abnormal	9	5	2	1
Death	0	0	22	12

Table 3. Comparisons of outcome between various groups of infants with grades I, II and III encephalopathy

	Grades I, II and III		Grades II and III						Grades I, II and III	
	All* (*n* = 301)		All* SVD (*n* = 43)		1976–1980 (*n* = 63)		1984–1988 (*n* = 44)		Levene *et al* (1985) (*n* = 122)	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Normal outcome	253	(84)	21	(49)	32	(51)	27	(61)	99	(81)
Severe handicap	14	(5)	7	(16)	9	(14)	5	(11)	9	(7)
Death	34	(11)	15	(35)	22	(35)	12	(27)	14	(12)

Results are number of infants (%).
SVD = spontaneous vaginal delivery.
*All refers to both 5-year periods together.

second it was. The Dublin study (Macdonald *et al.* 1985) indicated that the introduction of more intensive fetal monitoring resulted in a fall in the number of infants with neonatal seizures and persistent abnormal neurological signs. Our observations support that conclusion, a clear association being found between grades II and III encephalopathy and operative delivery, often with low Apgar scores. Most of these operative deliveries were undertaken for fetal distress.

However, abnormalities on the fetal cardiotocograph have not been found to be good predictors of hypoxic-ischaemic encephalopathy in the newborn period or of subsequent permanent brain damage, as many of those who have abnormal traces do not have subsequent problems and many who proved to have disability did not have abnormalities on the fetal heart monitor. Furthermore, recognition of abnormal fetal heart rate patterns and appropriate action resulting in delivery within 60 min of the onset of the abnormal pattern frequently fails to prevent the development of encephalopathy (Keegan *et al.* 1985).

The outcome of grade I encephalopathy was excellent in both time periods. The majority of infants with grade III encephalopathy died. It is these infants and those with grade II encephalopathy, of whom approximately 20% were left with serious handicap, that need further analysis.

Despite the overall fall in the number of affected infants in the two 5-year periods, the absolute numbers of infants with severe encephalopathy (grades II and III) who were born by unassisted vaginal delivery remained unchanged (23 in 1976–1980 and 20 in 1984–1988). Eighteen of these 43 infants had grade III encephalopathy. A number of these infants did not need active resuscitation and 25 had Apgar scores >5 at 5 min. However, 15 of these infants died and seven developed severe handicap.

The period of apparent near normality shown in these infants, as suggested by their satisfactory Apgar scores, has also been seen in infants who developed hypoxic-ischaemic encephalopathy following near-miss sudden death syndrome (Constantinou *et al* 1989). Thus it seems possible that an infant may suffer a severe cerebral insult before birth and yet show a satisfactory response at birth.

Hypoxic-ischaemic encephalopathy was first used as an assessment of asphyxia at birth by Sarnat & Sarnat (1976). It is a clinical syndrome that is seen following fetal distress and a poor response to birth by the infant. In those severely affected infants that die there is evidence of ischaemic brain damage at post-mortem examination. Less severely affected infants can be shown to have cerebral oedema, cerebral infarcts and haemorrhages by ultrasound and CT scans. Grading of this condition has provided one of the best predictors of outcome of asphyxiated infants (Levene *et al.* 1986). In the present study we have found the same group of clinical signs in infants in whom there was no recorded evidence of fetal distress and who made a good response to birth.

Whilst it cannot be certain that these infants have suffered hypoxia or ischaemia, this remains the most likely explanation, but the stage at which this insult occurs is not known. In these cases it was not detected by the current monitoring systems during pregnancy or labour and there may be an alternative explanation for the encephalopathy in these infants.

The Apgar scores at 5 min for those infants who subsequently developed grades II and III encephalopathy, irrespective of mode of delivery, were higher in the second period of study. This may represent more rapid and effective resuscitation. Unfortunately this improvement is not reflected in the outcome of these infants, which is not significantly different for the two periods. In fact, there have been numerous studies showing that the Apgar scores at 5 min, whilst more likely to be low in infants who later develop hypoxic-ischaemic encephalopathy, is not invariably so and is a poor predictor of subsequent brain damage (Levene *et al.* 1986; Nelson & Ellenberg 1981; Finer *et al.* 1983).

This study shows that a significant number of infants had major brain problems in terms of severe encephalopathy that was not anticipated by signs before birth, nor from their response to birth, and which later resulted in death or major permanent handicap. The aetiology and pathology of this group of infants remain uncertain. Although, as a group, relatively few in number, they require further research.

Finally, the quality of perinatal care has traditionally been assessed by the perinatal mortality rate. The increasing influence on the rate of the birth of very immature infants and the lack of correlation between the perinatal mortality rate and the incidence of cerebral palsy has led some to question its usefulness (Field *et al.* 1988; Jarvis *et al.* 1985). It is possible that incidence of hypoxic-ischaemic encephalopathy, especially grades II and III, will prove to be a more sensitive measure of perinatal care in term infants and provide a useful component of audit of the perinatal services.

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Received 17 May 1991
Accepted 20 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 392–394

GYNAECOLOGY

Abdominal irradiation in childhood; the potential for pregnancy

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ABSTRACT

Objective To investigate the impact of premature ovarian failure due to whole abdominal radiotherapy (DXT) in childhood on uterine physical characteristics and blood flow and measuring the uterine response to exogenous sex steroid replacement
Design A comparative observational study
Subjects 10 women with premature ovarian failure due to treatment with whole abdominal irradiation in childhood. A comparison group of 22 women with premature ovarian failure who had not received whole abdominal DXT.
Main outcome measures Uterine length and uterine blood flow measurement plus serial assessment of endometrial thickness during a cycle of exogenous sex steroid replacement.
Results Uterine length was significantly less ($P<0\cdot01$) in women who had been exposed to whole abdominal DXT in childhood (mean 4·1 cm, 2SE 0·8) compared with a mean of 7·3 cm (2SE 0·6) in the comparison group. The three women in the DXT group who were studied serially had no increase in endometrial thickness in response to physiological sex steroid replacement therapy and most of the 10 irradiated women had no detectable uterine blood flow with Doppler ultrasound.
Conclusions Uterine musculature and blood flow are irreversibly affected by high dose irradiation in childhood. Non-invasive assessment of this nature may predict potential for pregnancy following ovum donation and embryo transfer.

As a consequence of improved survival for children with neoplastic conditions, an increasing number of adolescent girls are facing a future with no ovarian function. Wallace *et al.* (1989) observed that 70% of girls who received 20-30 Gy whole abdominal radiotherapy (DXT) experienced pubertal failure and 26% a premature menopause. Even in the minority who retain ovarian function after abdominal DXT and who are fertile, the babies are often of low birthweight and there is increased perinatal mortality (Li *et al.* 1987).

With developments in assisted reproduction and the availability of donated oocytes, pregnancy is now possible for young women with absent ovarian function (Lutjen *et al.* 1984; Serhal & Craft 1987).

We have investigated the physical dimensions and blood flow of the uterus in women who have premature ovarian failure after abdominal radiotherapy in childhood and measured the response to exogenous sex steroid replacement.

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Patients and methods

Ten women with premature ovarian failure who had received whole abdominal DXT for malignant disease in childhood were studied (DXT-group). Their median age was 24 (range 15–31) years (Table 1). Each of these women had required exogenous sex steroid replacement to take them through puberty. A comparison group consisted of 22 women with premature ovarian failure who had not received whole abdominal radiotherapy (non DXT group). They had a median age of 31 years (range 23–37). In the non-DXT group, six women had primary amenorrhoea (primary ovarian failure), two of whom had Turner's syndrome (XO). The others in this group presented with secondary amenorrhoea. All the women in both groups received cyclical exogenous sex steroid replacement therapy and experienced withdrawal bleeding.

All women had an initial 'baseline' ultrasound assessment which recorded uterine length, endometrial thickness and uterine artery pulsatility index (PI). This initial scan was conducted while all the women in both groups were receiving standard schedules of cyclical sex steroid replacement. Ultra-

Table 1. Age at time of whole abdominal irradiation (DXT) and at study, primary diagnosis and radiation dose in 10 women with premature ovarian failure

Patient no.	Age at irradiation (years)	Age at study (years)	Primary diagnosis	Dose of DXT (Gy)
1	3	25	Wilms' tumour	30
2	5 weeks	18	Neuroblastoma	20
3	2	15	Yolk sac tumour	20
4*	2	31	Wilms' tumour	25
5	6	24	Wilms' tumour	30
6*	4	26	Wilms' tumour	30
7*	11	25	Ovarian dysgerminoma	30
8	2	16	Wilms' tumour	30
9	9	20	Non Hodgkin's lymphoma	20
10	11 months	24	Adrenal carcinoma	20

*Three patients who had serial assessments during one cycle of exogenous sex steroid supplementation.

sound measurements were recorded with an Acuson 128 Computed Sonography System, using a 3·28 MHz mechanical sector abdominal probe.

Uterine length

This was recorded in the longitudinal plane from the top of the fundus to the internal os.

Endometrial thickness

This was recorded as the measured distance in mm between myometrial/endometrial junction on either side of the mid uterine cavity (reported as double endometrial thickness).

Uterine artery PI

This index of the blood flow velocity wave form (Gosling 1976; Long *et al.* 1989) provides an indication of the impedance to blood flow in a vessel distal to the point of measurement. It is calculated as

$$\mathrm{PI} = A - B/\mathrm{Mean}$$

where A is the maximum velocity change in systole, B is the minimum change in velocity during diastole and the mean is the average velocity change. The ascending branch of the uterine artery is localized in the region of the internal os and the pulsed Doppler mode records change in velocity.

Eighteen women in the non-DXT group and three women in the DXT group (Table 1) had serial weekly ultrasound assessment during a cycle of exogenous steroid replacement with transdermal oestradiol and self-administered vaginal progesterone. The steroid replacement regimen was intended to provide physiological serum levels of oestradiol and progesterone (Critchley *et al.* 1990). Oestradiol supplementation (Estraderm 50, Ciba-Geigy, UK) was increased from a maintenance dose of one patch (delivering 50 μg/24 h) in a stepwise fashion to three patches (150 μg/24 h) and these were changed twice weekly. Vaginal progesterone was given 14 days after the start of oestradiol replacement either as Cyclogest (Hoechst, UK) 200 mg twice daily or Utrogestan (Besins Iscovesco, France) 100 mg thrice daily. Serum samples were collected three times weekly for estimation of oestradiol and progesterone concentrations, throughout the 28-day cycle of steroid supplementation. Radioimmunoassay of serum oestradiol was by a specific kit method using ^{125}I-labelled oestradiol (Coat-A-Count, Diagnostic Products Corp, Los Angeles, CA) and progesterone as described by Ratcliffe *et al.* (1982). Statistical analysis of uterine length employed Student's *t* test. Analysis of variance (ANOVA) was used to assess the change in endometrial thickness in response to steroid supplementation.

Results

Uterine length

In the DXT group the mean uterine length was 4·1 cm (2SE 0·8)(n = 10) compared with 7·3 cm (2SE 0·6) (n = 22) in the non-DXT group. In the latter group, measurements were comparable between the women with primary amenorrhoea and those with secondary amenorrhoea. Uterine length was significantly less ($P<0{\cdot}01$) in women who had been exposed to whole abdominal DXT in childhood.

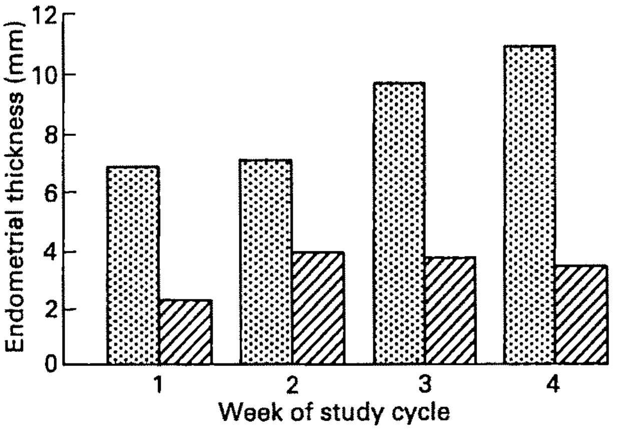

Fig. 1. Mean endometrial thickness during a cycle of exogenous sex steroid replacement in women with premature ovarian failure. ░ represents 18 women who had not been exposed to abdominal radiotherapy in childhood. ▨ represents three women who had been exposed to whole abdominal radiotherapy in childhood.

Mean endometrial thickness

During a 28-day cycle of exogenous sex steroid replacement a linear increase in endometrial thickness with time was observed (P<0·0001) among women in the non-DXT group (*n* = 18). The response was similar whether the amenorrhoea was primary or secondary. In contrast no change in endometrial thickness was recorded in the three women with premature ovarian failure who had had whole abdominal DXT in childhood (Fig. 1). This absence of increase in endometrial thickness occurred despite circulating oestradiol (393–974 pmol/l) and progesterone (15–58 nmol/l) levels within the physiological range. Serum levels of both these steroids were not significantly different from the women in the non-DXT group.

Uterine artery

There was an absence of any signal from either uterine artery in five of the 10 women in the DXT group and from one uterine artery in a further three women in this group. In contrast a signal was demonstrated in both uterine arteries in all the women in the non-DXT group.

Discussion

The observation that uterine length is significantly reduced in women with premature ovarian failure after whole abdominal DXT in childhood, compared with women with premature ovarian failure and not exposed to DXT, implies that prepubertal irradiation may have an irreversible effect on uterine development and vasculature. In these women the endometrium was unresponsive to physiological serum levels of oestradiol and progesterone and Doppler signals from the uterine artery adjacent to the uterus were absent in most. It is unclear whether this is a consequence of damage to the microstructure of the uterus and associated blood supply or to the sex steroid receptors. Thus, whole abdominal radiotherapy in childhood has the capacity to cause both ovarian failure and permanent uterine damage. Reports of live births in women who have been treated with whole abdominal radiotherapy are exceedingly rare and, in the report by Wallace *et al.* (1989), no patient carried a pregnancy beyond the second trimester. Appropriate vascularization and subsequent growth of the endometrium and uterus is essential for implantation and successful continuation of pregnancy. The ultrasound observations described here provide a simple non-invasive method for assessing the endometrial response to sex steroid stimulation in women with premature ovarian failure after whole abdominal radiotherapy. Such information seems essential before attempting pregnancy with a donated ovum.

Acknowledgments

We acknowledge the help of Dr Amanda Ogilvy-Stuart with this study and the technical assistance from Mrs C. A. Evans. Estraderm 50 was provided by Ciba-Geigy Ltd., UK. The Leukaemia Research Fund helped support the study.

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Received 19 July 1991
Accepted 20 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 395–398

GYNAECOLOGY

Epidermal growth factor receptor expression in normal endometrium and endometriosis: an immunohistochemical study

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ABSTRACT

Objective To study epidermal growth factor (EGF) receptor expression in endometrium throughout the menstrual cycle and to compare EGF-receptor expression in endometrium from patients with endometriosis with receptor expression in synchronously sampled endometriosis and in endometrium from healthy women.

Design An immunohistochemical study of receptor expression using murine monoclonal antibodies and timed endometrial and endometriotic biopsies.

Subjects 25 healthy women and 27 patients with a diagnosis of endometriosis.

Results Positive staining for EGF receptors was observed in 24 of 25 samples from normal women and in 26 of 27 endometrial samples from patients with endometriosis. In neither group was there any variation in the intensity of staining throughout the menstrual cycle and both glands and stroma were stained. EGF-receptor expression was observed in the glands of 15 out of 17 endometriotic lesions and in 12 of these biopsies positive staining was also present within endometriotic stroma.

Conclusion This study shows no difference in the intensity of staining of EGF receptors in endometrium throughout the menstrual cycle or between the glands of normal endometrium and those of endometriosis.

The pathogenesis of endometriosis is poorly understood. It has, however, long been accepted that endometriosis is an oestrogen dependent condition, being a disease of women of reproductive age. It has not been reported in premenarchal girls (Haney 1991) and in reports of endometriosis in postmenopausal women it has been related to the administration of exogenous oestrogens (Goodman *et al.* 1989). Exogenous oestrogens are also implicated in the occurrence of endometriosis in males with prostatic cancer (Oliker & Harris 1971; Pinkert *et al.* 1979) and in women with ovarian dysgenesis (Doty *et al.* 1980; Binns & Banerjee 1983).

In recent years it has become apparent that oestrogen action in the uterus may be mediated by the more localized autocrine and paracrine regulatory systems of the peptide growth factors, in particular epidermal growth factor (EGF). Oestrogen, acting through its transcription regulating receptor, increases both EGF binding and mRNA levels for the EGF receptor in uterine tissues (Mukku & Stancel 1985; Lingham *et al.* 1988). In cultured guinea pig fetal uterine cells, EGF stimulates progesterone receptor expression almost to the same extent as oestrogens (Sumida *et al.* 1988). EGF and other ligands for the EGF receptor are known to play a role in tissue differentiation in a variety of tissues such as the skin and the oestrogen responsive breast (Buick 1991). They may also play a role in the pathogenesis of endometriosis.

It is, therefore, of interest, to study EGF-receptor expression in endometrium as it develops and differentiates throughout the menstrual cycle and in the oestrogen dependent condition endometriosis. Receptors to EGF have been described in myometrium (Hofmann *et al.* 1984; Chegini *et al.* 1966; Berchuk *et al.* 1989a, b; Rees *et al.* 1990), endometrium (Hofmann *et al.* 1984; Sheets *et al.* 1985; Chegini *et al.* 1986; Taketani & Mizuno, 1988; Berchuk *et al.* 1989a, b; Bonaccorsi *et al.* 1989; Rees *et al.* 1990) and the endocervix (Sheets *et al.* 1985), but have not been described previously in endometriosis *in vivo*. We report here on EGF-receptor expression, demonstrated immunohistochemically, in the endometrium of both normal women and patients with endometriosis, throughout the menstrual cycle, and in endometriotic lesions.

Patients and methods

Endometrial samples were obtained from 25 healthy women and 27 patients with endometriosis, diagnosed at time of surgery, who underwent laparoscopy or laparotomy. All endometrial samples were obtained using the Pipelle suction curette ensuring all samples were obtained within 2–3 cm of the uterine fundus, thus avoiding the variation in receptor numbers along the length of the uterus that has been reported by Sheets *et al.* (1985). Biopsies of endometriotic lesions were obtained from 24 of the 27 patients with endometriosis.

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All women had a regular menstrual cycle of between 21 and 35 days and none had taken any hormonal preparation for 3 months before the study. The healthy women were either patients seeking sterilization or reversal of sterilization or infertile women where sperm dysfunction or tubal blockage was the only diagnosis. Women with unexplained infertility were excluded as endometrial development is retarded in 20% of such women compared with 3% of the normal population (Li *et al.* 1990). The diagnosis of endometriosis was made visually using the descriptions of endometriotic lesions reported by Martin *et al.* (1989) and Nisolle *et al.* (1990).

Forty-one of the women (22 healthy women and 19 patients with endometriosis) were recruited prospectively into the study and daily blood samples were taken from day 8 to day 17 of the menstrual cycle. Plasma oestradiol, progesterone and luteinizing hormone (LH) were measured. This regimen allowed precise timing of samples in the luteal phase of the cycle, relative to the LH peak, e.g., LH + 5 specifies a biopsy taken on the fifth day after the LH peak. Proliferative phase samples were dated from the first day of the last menstrual period. The regimen also allowed accurate assessment of the endocrine signal before the day of the biopsy. All the endocrine profiles fell within the normal ranges specified by Landgren *et al.* (1980). When endometriosis was discovered unexpectedly, at time of operation, or when healthy women were unable to attend for daily blood sampling, oestradiol and progesterone were measured on the day of biopsy only and the stage of the cycle determined on the basis of the steroid data and menstrual history. Oestradiol was measured using the DPC 2′ AB kit (Diagnostic Products (UK) Ltd), progesterone using DPC Coat-A-Count kit (Diagnostic Products) and luteinizing hormone using the LH MAIAclone kit (Serono).

Endometrial and endometriotic biopsies were embedded in Tissue Tek OCT compound (Miles Inc, Diagnostic Division), and frozen in pre-cooled isopentane (2-methyl butane) immersed in liquid nitrogen. All tissue samples were stored at −70°C until analyzed. Cryostat sections, 7 μm thick, were cut and mounted on poly L-lysine coated slides. Slides were air-dried briefly before fixing in acetone for 20 min. Slides were then rehydrated by washing three times for 10 min in TRIS buffered saline (TBS). Sections were then covered in a 1 in 5 solution of normal lamb serum in TBS (NLS) and, after 10 min, the excess serum was removed and the sections covered in a 1 in 40 dilution of the murine monoclonal antibody to EGF receptor in NLS (NCL-R1, Novocastra Laboratories, Newcastle upon Tyne, UK). The sections were incubated in a humidified chamber for 1 hour at room temperature before washing twice with TBS and applying the secondary peroxidase conjugated antibody (Dakopatts, P447) for 30 min at room temperature. Antibody complexes were localized using diaminobenzidine and hydrogen peroxide. No counterstain was employed and the stained sections were dehydrated through alcohols, cleared in xylene and mounted in DPX.

Serial sections were cut for staining with haematoxylin and eosin to permit histological study of the sample. Sections stained without monoclonal antibody acted as a negative control and allowed assessment of any nonspecific binding of the secondary antibody. In addition serial sections were stained with monoclonal antibodies to the oestrogen and progesterone receptor (NCL-ER, NCL-PR, Novocastra Laboratories). As these antibodies both give positive nuclear staining only, they acted as suitable additional negative controls against the membrane staining EGF-receptor antibody. Sections of placenta, known to express EGF receptor, were used as a positive control. Sections were scored as – (no staining greater than negative control), ± (when there was weak positive staining) and + (when there was obvious positive staining). All sections were scored independently by two observers (A.P. & B.J.R.).

Wilcoxon's signed rank test was used to test for any significant differences in staining between endometrium and synchronously sampled endometriosis.

Ethical permission for this study was obtained from the joint ethics committee of the Newcastle Health Authority and the University of Newcastle upon Tyne.

Results

EGF-receptor expression in the endometria of normal women

Positive staining for EGF receptor was detected in all 25 samples with weak staining observed in only one subject (LH+7). Fifteen samples were obtained during the follicular stage, ranging from day 4 to 16. The luteal phase samples were from days LH+1 to LH+7 with one luteal phase sample on day 21 where serial endocrine data were not available. Both glandular and stromal elements of the endometrium stained equally, with specific staining confined to the cell membrane. No variation in the intensity of staining was observed throughout the menstrual cycle.

EGF-receptor expression in the endometria of patients with endometriosis

Twenty-seven samples were studied from patients with endometriosis. Of these samples 15 were from the follicular phase of the cycle ranging from day 4 to day 12. There were six luteal phase samples from between days LH+2 and LH+11 inclusive, and a further six luteal phase samples (days 12, 16, 17, 21, 22 & 26) for which LH data were not available but steroid data (plasma progesterone) confirmed them to be from the luteal phase. Obvious positive staining was seen in 26 out of the 27 samples. Weak staining was seen in the sample from day 22. As in the endometria from normal women, staining was localized to the cell membrane, equal in glands and stroma and did not vary throughout the menstrual cycle.

EGF receptors in endometriotic lesions

Biopsies of endometriotic lesions were obtained from 24 of the 27 patients in whom endometriosis was diagnosed. Endometriotic glands and stroma were detected in 18 of the 24 specimens and in 17 of the sections stained for EGF receptor. The histological confirmation of endometriosis in this proportion of cases is in keeping with data from other studies (Cornillie *et al.*

1990). In 15 out of 17 sections obvious positive staining was observed in the glands of endometriosis and in 12 of these cases positive stromal staining was also observed. Of the seven biopsies where only stroma, characteristic of endometriosis, was present, positive staining was seen in only one. As in endometrium, staining was localized to the cell membranes and staining intensity did not vary with the menstrual cycle (Fig. 1).

Differences in the intensity of staining between endometrial and endometriotic glands was observed in only three patients. In two staining was absent in the endometriotic lesion. The third sample was from the same patient where weak staining had been observed in the endometrium; obvious staining was present in the endometriotic glands. In 11 of the 24 biopsies staining was absent in endometriotic stroma when it had been present in endometrial stroma ($P < 0{\cdot}01$). In 12 of the remaining patients staining was of equal intensity in endometrial and endometriotic stroma and the 13th patient was again the subject in whom weak staining had been observed in the endometrium.

Discussion

This study has shown immunohistochemically that EGF receptor is expressed in the glands and stroma of endometrium and endometriosis. There was no cyclical variation in the intensity of staining for EGF receptor in endometrium nor could we detect any difference in the intensity of staining between the glands of endometrium and endometriosis sampled synchronously from the same patient. EGF receptor expression in endometriotic stroma was detected in only 50% of the biopsies.

The presence of EGF receptor in both the glandular and stromal elements of endometrium has been reported previously (Hofmann *et al.* 1984; Sheets *et al.* 1985; Chegini *et al.* 1986; Taketani & Mizuno, 1988; Berchuk *et al.* 1989a, b; Bonaccorsi *et al.* 1989; Rees *et al.* 1990), but the biological significance of this observation remains in doubt. Controversy exists regarding variation in receptor expression throughout the menstrual cycle. Chegini *et al.* (1986) and Rees *et al.* (1990) studied five and ten women, respectively, and these numbers are obviously inadequate to draw firm conclusions. Taketani & Mizuno (1988) using a radio-iodinated EGF binding assay reported a rise in EGF binding from early to late proliferative phase with levels of binding reaching a plateau until between 4 and 6 days post-ovulation. They considered that the differences between their observations and those of Sheets *et al.* (1985), who showed no difference in binding between the proliferative and luteal phases of the cycle, could be explained because Sheets *et al.* (1985) divided their women into two groups on the basis of whether the samples had been obtained during the proliferative or luteal phase. This obscured any changes taking place within the proliferative and luteal phases. A similar argument could be invoked to explain the discrepancy between the immunohistochemical data of Berchuk *et al.* (1989a) and Taketani & Mizuno (1988). However, it is more likely that the semi-quantitative immunohistochemical method utilised both by us and Berchuk *et al* (1989a) is not sensitive enough to detect fluctuations in receptor expression during the menstrual cycle.

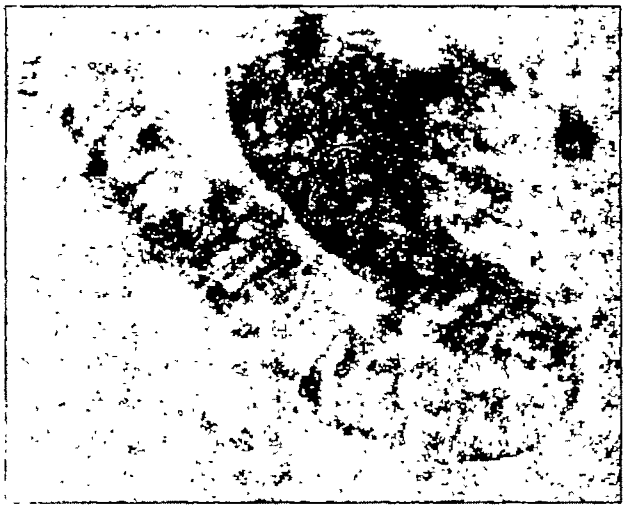

Fig 1. Epidermal growth factor receptor (EGFR) expression in endometriosis Positive staining for EGFR is seen in the cell membranes of both the glandular and stromal tissue.

The ligands for EGF receptor are potent mitogenic polypeptides and might be expected to play a role in the pathogenesis of the oestrogen-dependent condition endometriosis. The histogenesis of endometriosis remains in doubt, but circumstantial evidence supports an endometrial origin for the condition. Differences in EGF receptor expression in endometria from normal subjects might be expected if the receptor ligands played a significant role in the pathogenesis of endometriosis. No differences in staining intensity have been observed and it is therefore unlikely that there exist large differences in receptor expression between the endometria of normal subjects and the endometria of patients with endometriosis.

We are unaware of any previous description of EGF-receptor expression in endometriosis although EGF receptor expression has been reported in cultured cells from endometriotic lesions (Taketani 1989). EGF-receptor expression is thus yet another similarity between endometrium and endometriosis. Although detectable in most endometriotic lesions, EGF receptors were not always present within endometriotic lesions or within both glandular and stromal components. The significance of this observation is unclear, although it might suggest that endometriosis is responding incompletely to the endocrine environment as has previously been observed in ultrastructural studies (Schweppe *et al.* 1984).

It would appear that abnormal expression of EGF receptor in either endometrium or endometriotic lesions does not play a role in the pathogenesis of endometriosis. However, the observation of EGF-receptor expression, itself a marker of cellular differentiation, in endometriosis provides further circumstantial evidence for an endometrial origin for endometriosis. If any of the ligands for EGF receptors play a role in the pathogenesis of endometriosis such an effect is not dependent upon receptor over-expression.

Acknowledgments

This research was supported by the research committee of Newcastle Health Authority and further supported by a grant from the Peel Medical Research Trust.

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Received 19 July 1991
Accepted 19 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 399–401

GYNAECOLOGY

An objective and subjective assessment of uterine blood loss in postmenopausal women on hormone replacement therapy

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ABSTRACT

Objective To determine the volume of withdrawal blood loss in women taking hormone replacement therapy (HRT).

Design Prospective randomized double blind cross-over trial.

Subjects Twenty-nine postmenopausal women, with climacteric symptoms.

Interventions The women were treated with cycles of 2 mg oestradiol valerate for 21 days combined with either 250 µg levonorgestrel or 10 mg medroxyprogesterone acetate, for the last ten days. Each woman was randomly allocated to one of the preparations and switched to the other after four months.

Main outcome measures Uterine blood loss was estimated by the alkaline haematin method. Bleeding patterns were recorded specifying the number of days with bleeding and subjective rating of the amount of blood lost.

Results and conclusions The mean uterine blood loss was 35·2 ml and was equivalent to the normal menstrual blood loss. There was no significant difference between therapies but the women themselves considered that they bled more heavily when taking the levonorgestrel combination. The intraindividual variation in blood loss was small, independent of preparation taken, but the variation between individuals was large. Withdrawal bleeding started 2–3 days earlier when the women used the medroxyprogesterone acetate compared to the levonorgestrel formulation.

Many women suffering from climacteric symptoms are advised to take hormone replacement therapy (HRT). Previous studies have shown that treatment with oestrogen alone increases the risk of hyperplasia and carcinoma of the endometrium (Smith *et al.* 1975). This risk may be eliminated by adding a progestogen to the oestrogen treatment (Persson *et al.* 1989). The type and the duration of progestogen therapy probably affects women's feeling of well-being, the appearance of the endometrium and bleeding patterns. Most women (90%) taking sequential or cyclic oestrogen-progestogen therapy will have regular withdrawal bleeds (Whitehead *et al* 1978). Some women using HRT report heavy bleeding, but the correlation between subjective and measured blood loss, at least in younger women, is known to be poor (Hallberg *et al.* 1966). It was reported that 9–14% of healthy menstruating women have menorrhagia (Eijkeren *et al.* 1989), defined as a menstrual blood loss >80 ml, but to our knowledge, no previous trial has investigated withdrawal blood loss during HRT in postmenopausal women.

This study was designed to measure blood loss objectively during HRT and to study the influence of two different progestogens.

Subjects and methods

The study included 29 women who attended our outpatient clinics mainly because of vasomotor symptoms, such as hot flushes and sweats. Their mean age was 52·5 (SD 5) years and, on average, they had been without regular periods for 5·2 (SD 5) years. At least 6 months had elapsed since the last menstrual period in each woman. Twenty-three women had taken HRT previously and they were subjected to a wash-out period of 4–6 weeks before entering the study. Three women discontinued after 1, 8 and 10 weeks of treatment because of minor discomforts such as bleeding disturbances or lack of symptom alleviation. All the women gave their written informed consent. The study was approved by the ethics commitee of the Faculty of Medicine, University of Göteborg.

Hormone therapy

Two oestrogen-progestogen combination regimens were used. Each consisted of 2 mg oestradiol valerate (E2V) per tablet taken daily for 3 weeks out of 4. The progestogen component was added during the last 10 days and consisted of either 250 µg levonorgestrel (LNG), or 10 mg medroxyprogesterone acetate (MPA), daily. The study was designed in a double-blind, cross-over fashion. Each woman was allocated, using random numbers, to one of the formulations and switched to

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the other after 4 months. The physicians and the women were not aware of the treatment sequence until all data had been analysed. The tablets and the packages containing the tablets looked the same.

Protocol

All the women had a physical examination, including an endometrial biopsy, before starting therapy and on days 19–21 after 4 and 8 months of treatment. Endometrial biopsies were taken using either a Mi-Mark helix or a Vabra currette and the histological sections were examined by light microscopy. Bleeding patterns were recorded continuously by all the women, specifying the number of days with bleeding and each woman's own daily rating of the amount of blood lost. The woman attributed a score of 3 if she considered her blood loss to be as during a menstruation, 2 if the bleeding was small, 1 for spotting and 0 if there was no bleeding at all.

The blood loss during withdrawal bleeding was measured in treatment months 2 and 3 for each formulation, as described by Hallberg & Nilsson (1964) and modified by Newton *et al.* (1977). The vaginal tampons and sanitary towels were collected in plastic bags. The determination of blood loss was based upon the formation of alkaline haematin after the blood had been extracted from vaginal tampons and sanitary towels by NaOH in an automatic Stomacher Lab-Blender 3500.

Statistics

Conventional methods were used for calculating the mean and standard deviation. The Mann-Whitney *U*-test and Wilcoxon signed rank test were used to compare differences during treatment. The Spearman rank correlation coefficient was used to measure correlation between blood losses and bleeding scores. A *P*-value <0·05 was considered statistically significant.

Results

Bleeding patterns

All but two women experienced uterine withdrawal bleeding. There were wide inter-individual variations in blood loss (mean variation 87 ml), but the intra-individual variation was small (mean variation 26 ml) (Table 1). The mean blood loss during the two oestrogen-progestogen treatments are shown in Table 2. No significant difference in the measured blood loss could be detected between the two formulations (Wilcoxon signed rank test). However, the subjective ratings of the blood loss were higher when the levonorgestrel containing preparation was given (Table 3). The mean duration of bleeding each month was 3·8 (SD 2·1) and 3·6 (SD 2·5) days for the LNG and MPA preparations, respectively (*P*>0·05).

Table 1. Blood loss distribution during withdrawal bleeding in 26 postmenopausal women treated with two different oestrogen-progesterone regimens (MPA and LNG)*

Blood loss with MPA (ml)	Blood loss with LNG (ml) 0–20	21–40	41–60	61–80	>80	No. of women
0–20	11	4				15
21–40		3		1		4
41–60	1		1	1		3
61–80				1		1
>80					3	3
No. of women	12	7	1	3	3	26

*LNG = 2 mg oestradiol valerate and 250 µg levonorgestrel.
MPA = 2 mg oestradiol valerate and 10 mg medroxyprogesterone acetate.
The number of women are distributed in different blood loss ranges according to average blood loss from two consecutive monthly measurements.

The onset of withdrawal bleeding after the last tablet occurred after 3·1 (SD 2·2) days after administration of the LNG and after 0·4 (SD 3·2) days with the MPA formulation, $P<0{\cdot}02$ (Wilcoxon signed rank test).

Endometrial histology

Endometrial hyperplasia or atypia was not found in any of the women in this study. There was no difference in the histopathological appearance of the endometrium in the two groups and no significant correlation between the histopathological appearance of the endometrium during treatment month 4 and the amount of uterine bleeding during treatment months 2 and 3 could be demonstrated.

Discussion

Uterine blood loss is considered scanty in postmenopausal women taking oestrogen-progestogen combinations (Gambrell 1987). However, to our knowledge there have been no studies in which blood loss was measured objectively during HRT. Population studies in women of fertile age have given detailed information on menstrual blood loss, which is approximately 30–40 ml each month (Hallberg *et al* 1966). Small variations between different age groups have been reported (Hallberg *et al.* 1966). However, blood loss in menstruating women in the 50-year age group was higher than that in younger women (Hallberg *et al.* 1966; Rybo *et al.* 1985). In the present study, most postmenopausal women given cyclic HRT had withdrawal bleeding that was less than the menstrual blood loss in menstruating women. However, the mean volume lost was 35·2 ml, because some of the women had a heavy blood loss. Three had a blood loss of more than 80 ml, and this corresponds fairly closely to the frequency of menorrhagia in menstruating women (Eijkeren *et al* 1989).

It is tempting to speculate that there might be a relation between endometrial histology and the quantity of withdrawal bleedings. Padwick *et al* (1986) showed that women taking 'weak' progestogens started withdrawal bleeding earlier than women taking 'stronger' progestogens and that the endometrium appeared to be predominantly proliferative in women taking 'weak' preparations We could not find any correlation between blood loss and endometrial appearance. It should be noted that blood loss measurements and endometrial curettages were not performed the same treatment month, so that the biopsy did not affect the blood loss. However, women taking the MPA combination started their withdrawal bleeding 2–3 days earlier than those taking the LNG combination, indicating that the latter preparation had a stronger progestogenic 'potency' than the former.

Table 2. Blood loss during two treatment months of oestrogen-progestogen therapy in 23 postmenopausal women*

Progestogen	Blood loss (ml) Treatment month 2	Treatment month 3	Mean	Median	Range
Levonorgestrel	40·1 (8)	34·4 (7)	37·2 (7)	22·0	0–582
Medroxyprogesterone acetate	35·8 (11)	30·4 (10)	33·1 (10)	15·6	0–346

Results are mean (SEM) values where appropriate.

*Three of the 26 women were excluded from the analysis, two had no withdrawal bleeding and one missed a sample occasion.

There were large differences in blood loss between individuals but variation in individual women was small, irrespective of progestogen given. These findings are in agreement with previous studies by Hallberg *et al.* (1964 and 1966) in menstruating women. The type of progestogen, in the doses given, did not influence menstrual blood loss.

The subjective estimation of menstrual blood loss is not precise (Hallberg *et al.* 1966). However, in our study the subjective ratings of blood loss were higher when the levonorgestrel containing preparation was given. The reason for this discrepancy is not apparent. It is not known if variables such as the total blood loss, the number of days with bleeding or the intensity of bleeding during the first days affect the subjective scoring. Different progestogens may have a different effect on the psychological well-being of women, and this might influence the subjective judgement of withdrawal bleeding.

Two of the three women who bled more than 80 ml had a history of heavy menstrual blood loss having undergone curettage or having used tranexamic acid. It is possible that women who have a heavy menstrual blood loss before the menopause have withdrawal bleedings on HRT that are above average. The haemostatic mechanisms of the endometrium may be independent of the source of sex steroids, whether these are endogenously produced hormones in fertile women or exogenously administered hormones in the postmenopausal period. Rybo *et al.* (1985) reported that the menstrual blood loss was significantly elevated in 33 women at the age of 50 compared to when they were 38 and 44 years of age. Studies on blood loss in women before their menopause compared to the amount of withdrawal bleeding later during HRT would be of interest. If a correlation could be demonstrated, such data, together with the menstrual history, could predict the blood loss to be expected during HRT.

Table 3. Number of women and their subjective bleeding score during three months treatment with two different oestrogen-progestogen combinations

Bleeding score	LNG treatment month 1	2	3	MPA treatment month 1	2	3
<1	7	4	6	7	9	10
1–<2	2	3	3	7	5	7
2–<3	14	15	12	8	8	5
3	3	4	5	4	4	4

LNG = 2 mg oestradiol valerate and 250 μg levonorgestrel.

MPA = 2 mg oestradiol valerate and 10 mg medroxyprogesterone acetate.

Bleeding score: 0 = no bleeding; 1 = spotting; 2 = small bleeding; 3 = menstrual-like bleeding.

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Received 1 June 1990
Resubmitted 22 November 1991
Accepted 27 January 1992

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 402–407

GYNAECOLOGY

The epidemiology of hysterectomy: findings in a large cohort study

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ABSTRACT

Objective To examine patterns of hysterectomy in the Oxford-Family Planning Association (Oxford-FPA) study in relation to age, parity, social class and calendar period (–1974, 1975–79. 1980–84, 1985–89).

Design The Oxford-FPA study is a large scale prospective study of 17 032 women recruited from 1968–74 and still under observation.

Setting Seventeen family planning centres throughout England and Scotland.

Subjects At recruitment the 17 032 women were all white, British, married, aged 25–39 and willing to co-operate. In addition, they were using the pill or an intrauterine device or a diaphragm as their method of contraception.

Main outcome measure Hysterectomy rates per 1000 woman-years of observation in various subclasses of the data.

Results Up to the end of 1989, 1885 (11·1%) of the 17 032 women in the study were known to have undergone hysterectomy. Fibroids were the most common cause followed closely by menstrual disturbances in the absence of fibroids (hereafter referred to as 'menstrual disturbances'). Social class had a modest influence on hysterectomy rates. Hysterectomy for fibroids, prolapse, endometriosis and 'other reasons' showed little trend with calendar period while hysterectomy for menstrual disturbances and for cancer showed a sharp increase with calendar time especially at ages 30–39. Hysterectomy generally tended to increase with age and showed a strong relation to parity; in particular, hysterectomy for fibroids fell with parity and hysterectomy for menstrual disturbances rose sharply with parity. Using lifetable methods, it was estimated that almost 20% of the women in the study would have had a hysterectomy by age 55.

Conclusions The results give insights into factors affecting hysterectomy rates. Of particular interest is the modest influence of social class, the strong influence of parity and the rise in rates with calendar time at ages 30–39 for those undergoing hysterectomy for menstrual disturbances or cancer, but since the cohort is not directly representative of the population, some caution is required in extrapolating these findings. The estimated hysterectomy rate of about 20% by age 55 is in line with other similar estimates for the United Kingdom.

The rates of hysterectomy vary up to sixfold between countries with England & Wales having a relatively low rate (McPherson 1989). This operation remains variable between neighbouring health districts (McPherson *et al.* 1982) and, clearly, the determinants of hysterectomy are of considerable interest from an epidemiological and health policy perspective. Previous investigations of common surgical operations have failed to confirm an often quoted strong role of patient demand in determining the decision to perform a hysterectomy so other factors must be involved (Coulter & McPherson 1985).

Some information about patterns of hysterectomy is obtainable from routine sources such as the Hospital In-Patient Enquiry (see for example Teo 1990), but the diagnostic and procedural coding is undertaken by lay clerks, information about social class is unavailable or incomplete, and annual surgical rates take no account of the proportion of women who have already undergone hysterectomy and are therefore no longer at risk. Further information has been derived from a number of special studies, but these have tended to be small in size and of limited applicability. Accordingly, we decided to study the patterns of hysterectomy in the Oxford-Family Planning Association (Oxford-FPA) contraceptive study, taking into account the effects of calendar period, social class, age and parity. The Oxford-FPA study is of large size (17 000 women), the participants have been followed up annually with a high level of compliance over a period of 20 years, and all diagnostic and surgical coding has been done by one medically qualified member of the team throughout (M.P.V.). These features of the study should contribute to the generation of highly reliable

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information about patterns of hysterectomy in this cohort. Since the cohort is not directly representative of the general population some caution is required in extrapolating the findings to other groups of women.

Subjects and methods

A detailed description of the methods used in the Oxford-FPA study has been given elsewhere (Vessey *et al.* 1976). In brief, 17 032 women were recruited at 17 large family planning clinics in England & Scotland between 1968 and 1974 inclusive. At the time of recruitment, each woman had to be: (a) aged 25–39 years, (b) married, (c) white and British, (d) willing to participate and (e) either a current user of oral contraceptives of at least 5 months standing or a current user of a diaphragm or an intrauterine device of at least 5 months standing without previous exposure to the pill. During follow-up, each woman is questioned by a doctor or nurse at return visits to the clinic and certain items of information are noted on a special form. These include details of pregnancies and their outcome, changes in contraceptive practices and reasons for the changes, and particulars of any referrals to hospital either as an outpatient or an inpatient. Diagnoses on discharge from hospital are confirmed by obtaining copies of discharge letters, summaries and pathology reports. Women who stop attending the clinic are sent a postal version of the follow-up form and, if this is not returned, are interviewed by telephone or at home. The work in each clinic is co-ordinated by a part-time research assistant and follow-up has been maintained with an annual loss rate for 'relevant' reasons (withdrawal of co-operation or loss of contact) of only about 0·4%.

On reaching the age of 45, each woman is allocated to one of three groups (a) oral contraceptives used for a total of 8 or more years, (b) oral contraceptives never used and (c) other durations of oral contraceptive use. Only the women in the first two groups are followed up from then on in the detailed way described above. The present analysis, however, is not concerned with the effects of contraceptive use and the data for women aged 45 or more have been considered in continuity with the data for younger women.

The main part of the analysis is based on the computation of woman-years of observation in the various groups of interest with the calculation of indirectly standardised rates by the method described by Vessey *et al.* (1976). Women have been censored from the analysis at the time of occurrence of any of the following events: (a) end of follow-up, (b) loss to follow-up, (c) hysterectomy. χ^2 tests for trend are based on methods described by Breslow & Day (1980).

Results

Up to the end of 1989, 1885 (11·1%) of the 17 032 women in the Oxford-FPA study were known to have undergone hysterectomy. This total includes operations undertaken in both the public and in the private sector (separate figures for the two sectors are not available). Table 1 shows the main reasons for the operation by age group determined after the pathologist had examined the excised organ. Clearly fibroids and menstrual problems in the absence of fibroids (hereafter referred to simply as menstrual problems) are by far the most important reasons for hysterectomy in all the age groups covered by the Oxford-FPA study. On a proportionate basis, fibroids become more important, and menstrual problems become less important, with advancing age.

The types of operative procedure undertaken, according to the main reason for the operation, are shown in Table 2. The findings are as expected, with vaginal hysterectomy predominating for prolapse, total abdominal hysterectomy without bilateral salpingo-oophorectomy predominating for fibroids and for menstrual problems, and more extensive procedures appearing with considerable frequency in the remaining groups.

Social class

Preliminary analysis of the data showed that hysterectomy rates (both for individual reasons and overall) according to husbands social class (Registrar-General's classification—assessed at entry of each woman to the study) were not materially confounded by age or by calendar period. Parity had a modest confounding effect with lower social class women being of slightly higher parity than upper social class women. Accordingly, the hysterectomy rates for the different social classes shown in Table 3 are adjusted for the effect of parity. It is apparent that social class is not a major determinant of hysterectomy rates in the Oxford-FPA study, although there were

Table 1. Main reason for hysterectomy by age group. Column percentages in parentheses

	Age group (years)				
Reason for hysterectomy	≤34	35–39	40–44	≥45	Total
Fibroids	22 (15·5)	139 (29·0)	313 (41·3)	251 (49·6)	725 (38·5)
Menstrual problems, no fibroids found	68 (47·9)	207 (43·1)	271 (35·8)	120 (23·7)	666 (35·3)
Utero-vaginal prolapse	6 (4·2)	34 (7·1)	41 (5·4)	42 (8·3)	123 (6·5)
Cancer* invasive & pre-invasive	15 (10·6)	32 (6·7)	28 (3·7)	31 (6·1)	106 (5·6)
Endometriosis	6 (4·2)	27 (5·6)	49 (6·5)	19 (3·8)	101 (5·4)
Other reason**	25 (17·6)	41 (8·5)	55 (7·3)	43 (8·5)	164 (8·7)
Total	142 (100·0)	480 (100·0)	757 (100·0)	506 (100·0)	1885 (100·0)

*CIN of cervix 58, invasive cancer of cervix 27, ovarian cancer 10, endometrial cancer 10, cancer of ill defined site 1.

**This is a very heterogeneous category with 39 separate main reasons. Of these, abdominal pain (31) and chronic cervicitis (14) were the commonest.

Table 2. Types of operative procedure undertaken by main reason for operation. Row percentages in parentheses

	Type of hysterectomy					
	Total abdominal			Subtotal abdominal		
Reason for hysterectomy	– BSO*	+ BSO	Vaginal	–BSO	+ BSO	Radical
Fibroids	580 (80 0)	110 (15·2)	28 (3·9)	7 (1 0)	0	0
Menstrual problems	558 (83·8)	48 (7·2)	60 (9·0)	0	0	0
Prolapse	9 (7·3)	0	114 (92·7)	0	0	0
Precancer and cancer	55 (51 9)	24 (22·6)	9 (8·5)	0	1 (0·9)	17 (16·0)
Endometriosis	60 (59 4)	33 (32·7)	7 (6·9)	0	1 (1·0)	0
Other	104 (63 4)	49 (29·9)	6 (3·7)	3 (1 8)	1 (0·6)	1 (0·6)
Total	1366 (72·5)	264 (14·0)	224 (11·9)	10 (0·5)	3 (0·2)	18 (1·0)

*BSO — bilateral salpingo-oophorectomy.

statistically significant trends towards higher rates in lower social classes for operations undertaken for menstrual problems and for 'other reasons' and a non-significant trend in the same direction for operations undertaken for precancer and cancer. In addition, there were non-significant trends in the opposite direction for operations undertaken for fibroids and for endometriosis.

Age and calendar period

Because the effect of social class on hysterectomy was relatively small and because there was little association between social class, age and calendar period, social class was not taken into account in analyses considering the influence of age and calendar period (up to 1974, 1975–79, 1980–84, 1985–89) on hysterectomy rates. The rates were, however, standardized for the effect of parity. After taking age and parity into account, no important trends in hysterectomy rates with calendar period were found for operations undertaken for fibroids, prolapse, endometriosis or 'other reasons'. Accordingly, Table 4 shows the hysterectomy rates by age for these four reasons adjusted only for parity. The rates increase steadily with age for operations undertaken for prolapse and for 'other reasons'. For fibroids, the rates rise steadily up to ages 45–49 after which there is a sharp fall. The pattern is similar for endometriosis save that the rate peaks a little earlier at ages 40–44.

Hysterectomy rates for menstrual problems are shown by age and by calendar period in Table 5. Once again, the data are adjusted for parity. There is a striking increase in the rates across the calendar periods at ages 30–34 and 35–39; by contrast, the rates are more or less stable at ages 40–44, while they show a considerable decline at ages over 45. This pattern necessarily implies that the rates by age vary markedly in the different calendar periods. The picture is compatible with hysterectomy for menstrual problems being undertaken more frequently at younger ages in more recent years. However, the unweighted means of the rates at ages 35–39, 40–44 and 45–49 in the calendar periods 1975–79, 1980–84 and 1985–89 are 3·57, 3·85 and 4·01 respectively, suggesting that there has been only a modest overall increase in rates with time.

Table 6 corresponds to Table 5, save that the data relate to hysterectomy for precancer and cancer. There is a tendency for the rates to rise with calendar period, but the effect is clearest in those aged 35–39. This pattern reflects treatment of cervical intraepithelial neoplasia, this condition being by far the commonest diagnosis in the precancer and cancer group (making up 55% of the hysterectomies). Age effects are modest in each calendar period.

In Table 7, the overall data for hysterectomy are shown by age and calendar period. There is a marked rising trend with calendar period at ages 30–34 and 35–39, but the rates are otherwise remarkably stable.

Parity

As indicated earlier, hysterectomy rates by parity are modestly

Table 3. Hysterectomy rates per 1000 woman years by husband's social class Numbers of hysterectomies in parentheses

	Husband's social class (Registrar Generals Classification)			χ^2	
Reason for hysterectomy	I–II	III	IV–V	(1) trend	*P*
Fibroids	2·91* (309)	2 74 (351)	2·48 (65)	1·5	0·22
Menstrual problems	2·12 (220)	2·88 (368)	2 72 (78)	8·8	0·003
Prolapse	0·46 (48)	0·48 (62)	0·46 (13)	0·0	0·91
Precancer and cancer	0·36 (38)	0·40 (51)	0·62 (17)	2·5	0·12
Endometriosis	0 47 (49)	0·34 (44)	0·30 (8)	2·6	0·11
Other	0·47 (49)	0·73 (93)	0·78 (22)	6·5	0·01
Total	6 80 (713)	7·57 (969)	7·39 (203)	3·2	0·07

*Rates standardized for parity (0, 1–2, ≥3 births).

Table 4. Hysterectomy rates per 1000 woman-years by age for fibroids, prolapse, endometriosis and 'other reasons'. Numbers of hysterectomies in parentheses

Age (years)	Reason for hysterectomy			
	Fibroids	Prolapse	Endometriosis	Other reasons
25–29	0·14* (3)	0·00 (0)	0·05 (1)	0·21 (4)
30–34	0·38 (19)	0·13 (6)	0·10 (5)	0·44 (21)
35–39	1·98 (139)	0·47 (34)	0·38 (27)	0·58 (41)
40–44	4·55 (313)	0·57 (41)	0·70 (49)	0·78 (55)
45–49	6·13 (196)	0·78 (26)	0·52 (17)	0·65 (22)
50+	3·21 (55)	0·86 (16)	0·11 (2)	0·15 (21)

*Rates standardized for parity.

confounded by social class, but the effect of adjustment is negligible. Likewise allowance for calendar period had no effect on the rates relating to fibroids, prolapse, endometriosis and 'other reasons' and only a small effect on the rates relating to menstrual disorders and precancer and cancer. Accordingly, we considered it reasonable to assess the effect of parity on hysterectomy rátes after standardizing for age alone. The data thus obtained are shown in Table 8. Hysterectomy rates for fibroids declined with increasing parity, but those for menstrual problems showed the opposite trend. As expected, hysterectomy for prolapse did not occur in nulliparous women. Hysterectomy for endometriosis showed little relation with parity while there was a modest increase in hysterectomy for precancer and cancer and for 'other reasons' as the number of children born rose. Overall hysterectomy rates also showed a modest positive association with parity.

Cumulative hysterectomy rates

Finally, cumulative overall hysterectomy rates per 100 women were estimated, using standard lifetable methods. Cumulative rates at age 30, 35, 40, 45, 50, and 55 were as follows 0·3, 1·8, 5·5, 11·5, 17·2 and 19·9.

Discussion

There are a number of sources of information about patterns of hysterectomy in the United Kingdom, most notably the Hospital In-patient Enquiry. None of these sources, however, includes such detailed and reliable information as that reported here. Nonetheless, the Oxford-FPA study cohort is not directly representative of the general population. Caution is therefore required in extrapolating the results more widely. Having said this, Alderson & Donnan (1978) estimated the cumulative hysterectomy rate based on the Hospital In-patient Enquiry at 19% by age 70, for women born in the 1940s. This figure compares closely with our own estimate for women aged 55.

The reasons for hysterectomy and the types of operative procedure undertaken were more or less as expected. The findings in relation to social class, however, were of considerable interest since there has been a lively controversy in the literature as to what extent hysterectomy rates are related to this variable (Coulter & McPherson 1986). Our data support the view that social class, while having some effect, is not a major determinant of hysterectomy. It should be remembered, however, that the women in the lower social classes in the Oxford-FPA study are not necessarily typical of lower social class women in general. In particular, every woman in the Oxford-FPA study had to be sufficiently motivated to attend a family planning clinic in order to be recruited. This may imply that the lower social class women included in the study tend to be those with middle class attitudes towards health and disease. Of the associations between hysterectomy and social class, the most impressive were with precancer and cancer and with menstrual disturbances. The association with precancer and cancer is undoubtedly attributable to the fact that precancer and cancer of the cervix is commoner in lower than in higher social class women (Mant *et al.* 1988). The association with menstrual disturbances is supported by the results of Morbidity Statistics from General Practice for 1981–82 in which the standardized

Table 5. Hysterectomy rates per 1000 woman-years for menstrual problems by age and calendar period. Numbers of hysterectomies in parentheses

Age (years)	Calendar period				χ^2 (1) trend	*P*
	–1974	1975–79	1980–84	1985–89		
25–29	0·21* (4)	0·26 (1)	–	–	0·0	0·86
30–34	0·96 (22)	1·41 (34)	2·04 (7)	–	3·7	0·06
35–39	1·76 (32)	2·81 (71)	3·68 (85)	5·74 (19)	20·6	<0·001
40–44	3·53 (20)	3·65 (73)	4·29 (98)	4·02 (80)	0.6	0·42
45–49	–	4·26 (21)	3·59 (51)	2·53 (32)	3·8	0·05
50+	–	–	1·44 (5)	0·81 (11)	1·1	0·30

*Rates standardized for parity.

– Signifies insufficient data for analysis.

Table 6. Hysterectomy rates per 1000 woman-years for cancer by age and calendar period. Numbers of hysterectomies in parentheses

Age (years)	Calendar period				χ^2 (1) trend	*P*
	–1974	1975–79	1980–84	1985–89		
25–29	0·05* (1)	0·22 (1)	–	–	1·2	0·28
30–34	0·14 (3)	0·35 (9)	0·26 (1)	–	1·2	0·28
35–39	0·17 (3)	0·28 (7)	0·75 (18)	1·12 (4)	11·4	0·001
40–44	0·36 (2)	0·41 (8)	0·39 (9)	0·44 (9)	0.1	0·79
45–49	–	0·20 (1)	0·56 (8)	0·73 (9)	1·7	0·19
50+	–	–	0·57 (2)	0·81 (11)	0·2	0·64

*Rates standardized for parity.
– Signifies insufficient data for analysis.

morbidity ratios for disorders of menstruation for classes I & II, IIIN, IIIM and IV & V, were 88, 95, 110 and 110 respectively.

Patterns of hysterectomy by age were, once again, not surprising, but the trends with calendar period revealed some interesting variation. These trends were stable over the 20 year period reviewed for hysterectomy for fibroids, prolapse, endometriosis and 'other reasons' as also noted in Scottish vital statistics by Teo (1990). An upward trend for precancer and cancer was not surprising in view of an increasing rate of detection of cervical intraepithelial neoplasia in the study over the years. The trend for menstrual disorders, however, with rising operation rates at young ages and falling rates at older ages was unexpected. Teo (1990) noted a general rise in rates for menstrual disorders in Scotland, but without our age pattern. Our data suggest that hysterectomy for menstrual problems has been done at younger ages in more recent years than in the past, with only a modest overall increase in the rates. It seems possible that recent studies which have shown the early work on the post-hysterectomy depression syndrome to be invalid (Gath *et al.* 1982) have encouraged doctors to suggest surgical treatment for young women with menstrual problems more readily than in the past.

The findings in relation to parity, while perhaps not surprising, were, nonetheless, very striking. Fibroids, as expected, were more important as a reason for hysterectomy in nulliparous than in parous women. The trend was, however, very strongly in the opposite direction for menstrual problems. When these two major reasons for hysterectomy were summed, the relation with parity was modest, rates rising from 4·46 per thousand woman-years for nullipara to 5·61 per thousand woman-years for women with three or more children. The findings on hysterectomy for prolapse were unremarkable but the absence of any relation between hysterectomy for endometriosis and parity is of interest.

It is important to remember that many factors influence surgical rates, especially when the operation concerned is an elective one. This topic has been reviewed by Coulter *et al.* (1988). In addition, the epidemiology of hysterectomy as described in this paper does not necessarily reflect the epidemiology of the conditions for which hysterectomy is undertaken. Hysterectomy, for example, is not a common treatment for cervical intraepithelial neoplasia, usually being reserved for older women with advanced disease or who also have troublesome menstrual symptoms. Likewise, the majority of women presenting with severe menstrual problems at a young age will be managed conservatively rather than by hysterectomy.

The data available so far suggest that cumulative hysterectomy rates will reach a high level in the Oxford-FPA study. Thus using lifetable methods, we estimate that almost 20% of women will have had a hysterectomy by age 55, and the actual figure may eventually turn out to be higher than this.

Acknowledgments

We would like to thank Mrs P. Brown, Mrs D. Collinge, Mrs J. Winfield, our research assistants and the doctors and nurses working in the participating clinics for their continued loyal support. We are also grateful to the Medical Research Council, the Imperial Cancer Research Fund and the Knott Family Trust for financial support.

Table 7. Hysterectomy rates per 1000 woman-years for all reasons combined by age and calendar period. Numbers of hysterectomies in parentheses

Age (years)	Calendar period				χ^2 (1) trend	*P*
	–1974	1975–79	1980–84	1985–89		
25–29	0·69* (13)	0·51 (2)	–	–	0·2	0·69
30–34	1·98 (44)	2·85 (70)	3·66 (13)	–	5·4	0·02
35–39	5·22 (91)	5·92 (148)	8·60 (206)	9.96 (35)	23·3	<0·001
40–44	10.43 (57)	10·00 (194)	11·56 (264)	11·69 (242)	2.5	0·12
45–49	–	11·33 (55)	12·84 (181)	11·47 (147)	0·0	0·83
50+	–	–	8·91 (31)	6·78 (92)	1·5	0·23

*Rates standardized for parity.
– Signifies insufficient data for analysis.

Table 8. Hysterectomy rates per 1000 woman-years by parity. Numbers of hysterectomies in parentheses

Reason for hysterectomy	Parity (number of live and still births) 0	1–2	3+	χ^2 (1) trend	*P*
Fibroids	3·94* (58)	2·95 (461)	2·31 (206)	15·4	<0·001
Menstrual problems	0·52 (9)	2·39 (382)	3·30 (275)	43·8	<0·001
Prolapse	0·00 (0)	0·49 (77)	0·52 (46)	3·2	0·07
Precancer and cancer	0·33 (6)	0·39 (62)	0·45 (38)	0·7	0·39
Endometriosis	0·24 (4)	0·42 (67)	0·35 (30)	0·0	0·92
Other reasons	0·49 (9)	0·58 (91)	0·77 (64)	3·6	0·06
All reasons	5·30 (86)	7·22 (1140)	7·65 (659)	7·4	0·006

*Rates standardized for age (25–29, 30–34, 35–39, 40–44, 45–49, 50+).

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Received 25 September 1991
Accepted 21 February 1992

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 408–411

REPRODUCTIVE SCIENCE

Study of the birthweight of parents experiencing unexplained recurrent miscarriages

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ABSTRACT

Objective To examine birthweight and preterm birth rates in couples with unexplained recurrent miscarriages.

Design A case control study. Birth data of couples with recurrent miscarriages were obtained from midwife records. Time and sex-matched births from the same records served as controls.

Setting A Regional Hospital in Denmark.

Subjects 79 singleborn women with recurrent miscarriages and 60 of their male partners comprised the main study groups. Two control groups comprised 474 female and 360 male singleborn infants who survived day 7 postpartum.

Main outcome measures Mean birthweight in the two main study groups and in subgroups with histories of 3, 4 and ≥5 miscarriages.

Results The mean birthweight of the women with recurrent miscarriages was 3265 g (SE 70) and in female controls 3414 g (SE 23) ($P<0{\cdot}025$). The 17 women with five or more miscarriages had a mean birthweight of 2991 g (SD 140) ($P<0{\cdot}001$ compared with controls). Of the women in the study group 10·8% were born preterm compared with 2·9% of the controls ($P = 0{\cdot}01$). The mean birthweight of the male partners in the study group, 3470 g (SE 68), did not differ significantly from that of 3504 g (SE 31) in the male controls ($P<0{\cdot}5$).

Conclusions Women suffering unexplained recurrent miscarriages have on average had a significantly lower than normal birthweight themselves, whereas this was not observed in their male partners. This points towards the existence of a birthweight-reducing trait associated with recurrent miscarriages, the trait being manifest only in the woman.

The aetiology of idiopathic recurrent miscarriages is in the main still unknown. There is growing evidence that immunological factors are involved in the pathogenesis of a proportion of the cases (Johnson & Ramsden 1988). It has been reported that, in their occasionally successful pregnancies, women with recurrent miscarriage give birth to infants who on average have a lower birthweight than expected (Alberman *et al* 1980; Reginald *et al.* 1987). This suggests an association between a factor causing low birthweight and a factor causing fetal loss in these women.

In the present case-control study we have collected data on the birthweights of 79 women with recurrent miscarriages, their husbands and appropriate controls. The object was (i) to investigate whether the risk of low birthweight was an inherited trait which could be traced to the parents of the lost fetuses and (ii) to examine whether the low birthweight trait was inherited from both or from only one of the parents.

Subjects and methods

Definitions

Recurrent miscarriage was defined as having had at least three consecutive fetal losses preceding entry to the study with no intermittent live births. Fetal loss was defined as either a miscarriage before 28 weeks gestation or an intrauterine fetal death after 28 weeks.

A preterm delivery was defined as a birth occurring before 37 completed weeks gestation measured from the first day of the last menstrual period.

Study group

A total of 103 couples with recurrent miscarriages were referred to our clinic between 1 June, 1986 and 1 January, 1990 from all over Denmark for participation in a randomized study to assess the efficacy of leukocyte immunization. All the previous miscarriages had been confirmed by histological examination or positive pregnancy tests. All women had proved to be normal when investigated by hysterosalpingography/hysteroscopy, measurement of midluteal serum progesterone in three cycles (normal value >25 mmol/l), measurement of serum-thyroxin (normal value 60–148 nmol/l) and karyotyping on peripheral blood. The male partners had been karyotyped and most of them had had a semen analysis. In our clinic, the women were subsequently screened for the lupus anticoagulant. Its presence was diagnosed when activated partial trom-

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boplastin time (APTT) was >40 s and as the confirmatory test, the tissue tromboplastin inhibition (TTI) ratio was >1·30 on at least two occasions a month apart. Four women with lupus anticoagulant were not included in the present study as they were not considered to have unexplained recurrent miscarriages.

The study groups comprised the individuals from those couples with unexplained recurrent miscarriages whose own birth data could be obtained from the midwife records in the Danish State Archives, where all completed midwife records are filed. Only three of the four archives covering Denmark gave us access to the data we required for the women with recurrent miscarriages, their husbands and the controls.

Questionnaires were mailed to all 103 women with recurrent miscarriages except for six who were known to be immigrants and the four who were positive for the lupus anticoagulant. The women were asked for information necessary to procure the records of their own birth: the place and time of the birth and name of mother. If the present male partner had been father to at least two of the woman's fetal losses, he was asked to give similar information. Partners were only included in the study if we succeeded in obtaining the birth data of the women. A total of 24 women and 19 male partners were either not eligible for the study or the necessary data could not be obtained (Table 1). Birth data for 79 women and 60 husbands, comprising 90% of the eligible women and 88% of the eligible husbands, were finally procured and these individuals formed the two main study groups. Thirty-five (25%) of the births had occurred in hospitals or birth clinics whereas the remaining were home confinements.

The women had a mean age of 30·3 years (range 21–39); with birth years ranging from 1949 to 1967. They had suffered a mean of 3·8 miscarriages (range 3–8). Of the 299 miscarriages 260 (87%) had been in the first trimester, 36 (12%) in the second trimester and 3 (1%) were third trimester intrauterine fetal deaths (all occurred before 33 weeks gestation).

Twenty-four women were secondary miscarriers having had at least one live born infant (usually in the first pregnancy) preceding at least three consecutive miscarriages. Two of these women had given birth to two live children. The remaining 55 women were suffering primary recurrent miscarriage and had had no previous live births. The nine eligible women who were not included in the study group had had a mean of 3·5 miscarriages (range 3–7).

The male partners included in the study group had a mean age of 32·6 years; their years of birth ranged from 1944 to 1967. Two of the male partners had fathered only two pregnancies that miscarried, whereas the other 58 had fathered three or more pregnancies that miscarried. All these data relate to the time when the couple had their first records taken in our clinic.

Table 1. Reasons for non-inclusion in the study groups of individuals from couples with recurrent miscarriages

	Women (n = 103)	Male partners* (n = 79)
Ineligible individuals		
Lupus anticoagulant diagnosed	4	
Born abroad	6	2
Questionnaire not answered	1	
Information insufficient	1	1
Twin	3	1
Fathered <2 miscarriages		7
Eligible individuals		
No access to relevant archive	6	5
Not found in archives	3	3
Birth data successfully procured	79	60

*Partners of women with birth data.

Controls

A control group for each of the two study groups was created from data in the midwife records. For each woman or male partner, the last three singleborn infants of the same sex born before, and the first three singleborn infants born subsequent to, the index birth were taken as controls. Only infants who were living 7 days postpartum were included in the control groups. The female control group comprised 474 individuals and the male control group 360 individuals.

Midwife records

The Danish midwife record contains information about the birthweight and the sex of the newborn infant. It records whether the infant was liveborn or stillborn and also if the infant died in the perinatal period (within 7 days after birth). Preterm birth together with the gestation was recorded from 1950. The midwife records are made individually by each midwife except in a few large maternity wards. The delivery data are entered chronologically and birthweights are recorded with an accuracy ranging from 10 to 50 g.

Statistics

Statistical analysis was by Student's two-tailed t-test for differences between means and by Fisher's exact test for differences between proportions, the latter being used because of groups wih small numbers. Odds ratios and their 95% confidence intervals (95% CI) were calculated by the method of Miettinen (Kirkwood 1988). A P-value <0·05 was considered significant.

Results

Figure 1 depicts the birthweight distribution of the study group and the controls. The mean birthweight of the women in the study group was 3265 g (SE 70) and that of the controls 3414 g (SE 23) ($t_{551\mathrm{df}}$ = 2·33, P<0·025). In the female study group 10·1% had a birthweight of <2500 g compared with 3·4% of the controls (P = 0·03, Fisher's test, odds ratio 3·2, 95% CI 1·5–7·5). The mean birthweight of the women with primary miscarriages was 3292 g (SE 71) and of those with secondary miscarriages 3196 g (SE 161) ($t_{77\mathrm{df}}$ = 0·64, P>0·5).

The mean birthweights of the male partners in the study group and those in the control group were 3470 g (SE 68) and 3504 g (SE 31), respectively ($t_{418\mathrm{df}}$ = 0·42, P>0·5). Low birthweight (<2500 g) was recorded in 1·7% of the male partners in the study group and in 3·1% in the male control group (P = 0·94, Fisher's test; odds ratio 0·54, 95% CI 0·1–4·1).

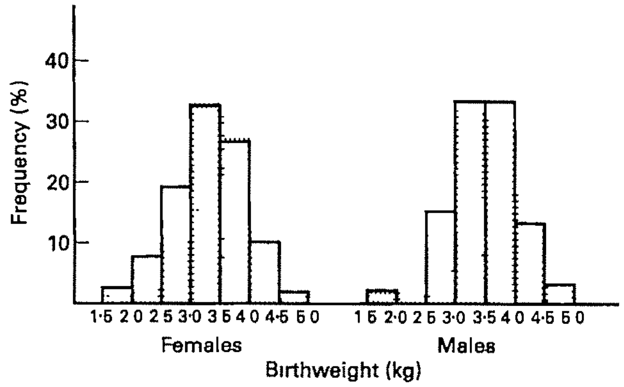

Fig. 1. Distribution by birthweight groups of 79 women with recurrent miscarriage, 60 of their male partners and 474 female and 360 male controls. White columns: women with recurrent miscarriages (left) or male partners (right). Shaded columns: women controls (left) and male controls (right).

The control group may be biased as it has not been adjusted for the differences in survival between the various weight groups after day 7. A statistical survey of infant mortality rates throughout the first year of life was performed for all Danish infants born in the 3-year period 1954–1957 (Danish Statistical Department 1960). This period is representative of the members of the control groups. The survey showed that 94·7% of infants who were alive on day 7 postpartum in the weight group 1500–1999 g survived their first year of life. In the weight groups 2000–2499 g, 2500–2999 g and ≥3000 g the corresponding figures were 97·5%, 98·7% and 99·2%. Adjusting for these weight-group-specific survival rates increases the mean birthweight of the female controls from 3414 g (SE 23) to 3416 g (SE 23) and of the male controls from 3504 g (SE 31) to 3513 g (SE 30) which causes no significant change in the statistical comparisons between the two study groups and controls (t_{551df} = 2·36 and t_{418df} = 0·53, respectively).

Figure 2 depicts individual birthweights in the study groups according to the number of previous miscarriages. The mean birthweight of the women with ≥5 miscarriages was 2991 g (SE 140) compared with 3414 g (SE 23) in the controls group (t_{489df} = 3·35, P<0·001). The figure also depicts the individuals in the study groups who, according to the midwife records, were born preterm. Data on preterm birth were available for 74 and 57 of the records of the women and the men respectively. Preterm birth had occurred in 10·8% of the women with recurrent miscarriage and in 2·9% of the female controls (P = 0·01, Fisher's test; odds ratio 4·0, 95% CI 1·7–9·5). Preterm birth had occurred in 1·8% of the male partners compared with 2·9% of the male controls (P = 1·0, Fisher's test; odds ratio = 0·6, 95% CI 0·1–4·6).

The mean birthweight of all 26 children (12 boys and 14 girls) born to women with secondary recurrent miscarriages in the study group was 3029 g (SE 140) which differed (t = 2·29, P<0·03) from the average birthweight of all singleton infants in Denmark born to women of parity one, which was 3349 g (SE 2) (The National Board of Health 1988).

Discussion

Previous studies have suggested an association between recurrent miscarriage and the risk of having babies with low birthweight. Alberman *et al.* (1980) found that women with a history of recurrent miscarriage gave birth to infants with a mean birthweight that was approximately 300 g lower than expected and the mean birthweight fell as the number of previous miscarriages increased. Reginald *et al.* (1987) found an increased rate of preterm birth and small-for-gestational-age infants in women with recurrent miscarriages who subsequently had a live birth. It has also been reported that the preterm birth rate increased with increasing number of previous miscarriages (Keirse *et al.* 1978; Pickering *et al.* 1985). Alberman *et al.* (1980) also reported that the mean birthweight of infants born *before* a miscarriage was lower than that of infants who were followed by another live birth. Because of their design, those studies provided information only on the subgroup of women who had given birth to at least one child and no information on birthweight of the woman or her partner were available.

The present study has demonstrated for the first time that women who suffer recurrent miscarriages tend themselves to have been born with a significantly reduced mean birthweight and this was valid for all the subgroups studied and not only those with secondary miscarriages. The greater the number of previous miscarriages, the lower did the average birthweight seem to be.

However, greater numbers of women in the subgroups are needed to be able to confirm this suggestion. Preterm birth may have been partly responsible for the lower mean birthweight of

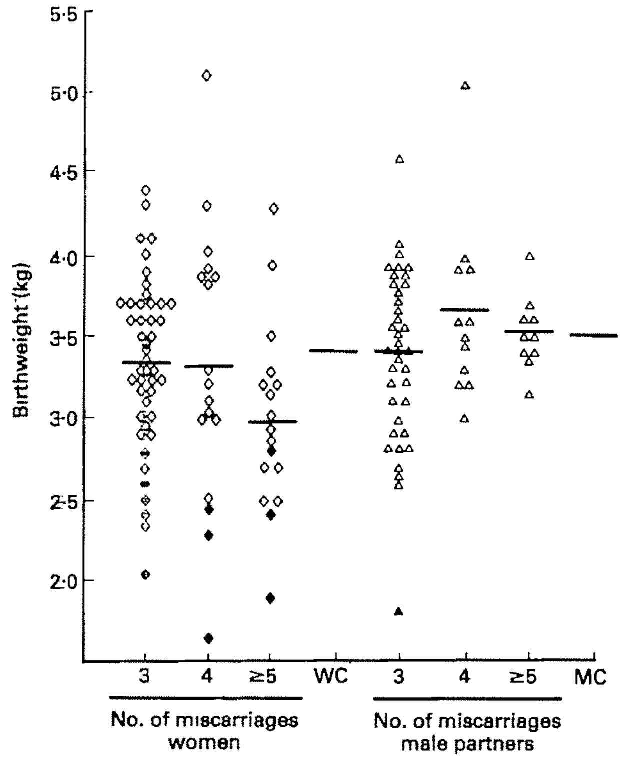

Fig. 2. Individual birthweights of 79 women (◇ ◆) with recurrent miscarriages and 60 of their male partners (△ ▲) according to the number of previous miscarriages experienced by the couple. Horizontal bars represent the mean for each group with recurrent miscarriages and for the women controls (WC) and men controls (MC). Solid symbols: preterm infants.

the women with recurrent miscarriages. Exact gestational ages were only recorded in the midwife records for infants born preterm. Consequently we were not able to estimate the proportion of small-for-gestational-age infants.

We consider the control groups as representative since they consist of sets of liveborn infants matched in time, sex and place with the members of the study group. Theoretically, the control groups would be more closely matched if the individuals who died between 7th day postpartum and reproductive age were excluded. However, adjusting for the expected birthweight-specific mortality rates in the first year of living merely results in insignificant changes in the mean weights. The exclusion of infants dying in the first 7 days postpartum seems to adjust for the major part of the bias and any remaining bias will tend only to underestimate slightly the mean birthweight of the controls.

As opposed to their wives, the mean birthweight and the proportion born preterm of the fathers of the unsuccessful pregnancies did not differ from controls.

The results of the study seem to indicate that the factor associated with the decrease in birthweight in offspring of couples with a history of recurrent miscarriage is located in the maternal genome. A paternal contribution of a low-birthweight-associated trait seems unnecessary for recurrent miscarriage to occur.

The genetic nature of the low birthweight trait remains unclear. However, from other studies there are some suggestions that the trait may be linked to the immune system. Maternal histocompatibility (HLA-)antigens in the siblings of women with recurrent miscarriages have been reported to be markers for the predisposition to give birth to infants with low birthweight (Christiansen *et al.* 1990). Seen in the context of recently identified antigens with possible immunological functions located on the trophoblast (Ellis *et al.* 1990; Kovats *et al* 1990; Risk *et al.* 1991) it is not unrealistic to believe that HLA and non-HLA-antigens on maternal immunocompetent cells and trophoblastic tissue respectively are involved in the normal development of pregnancy. Normal trophoblast invasion in the decidua have been reported to depend on cells from the immune system (Michel *et al.* 1990).

Further studies are needed to clarify the interactions of immunologic and non-immunologic nature which take place at the feto-maternal interface. We hope such studies will shed more light on the clinical association between recurrent miscarriage, low birthweight and preterm birth.

Acknowledgments

This study was supported by grants from the Research Fund of Aalborgs Frivillige Bloddonorer and the Research Fund of the County of Northern Jutland.

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Received 7 May 1991
Accepted 31 October 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 412–416

REPRODUCTIVE SCIENCE

Calcium homeostasis in pregnancy during long-term heparin treatment

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ABSTRACT

Objective To investigate the effect of subcutaneous heparin treatment on calcium homeostasis in pregnancy.

Design A longitudinal case-control observational study.

Setting Department of Obstetrics and Gynaecology, Karolinska Hospital, Stockholm, Sweden.

Subjects 36 pregnant women with previously verified thromboembolic complications and 23 healthy pregnant control women similar in age, parity, weight, and smoking habit.

Interventions Thromboprophylaxis during pregnancy and 6 weeks post partum was given with subcutaneous heparin twice daily to the 36 women with a history of thromboembolic complications, 16 received an average dose of 24 500 IU/day and 20 a mean dose of 17 300 IU/day. Venous blood and urine samples were obtained every 4 weeks.

Main outcome measures Serum concentrations of total calcium, ionized calcium, calcitonin and urinary calcium.

Results Women on high-dose heparin treatment showed significantly higher concentrations of total and ionized calcium and of calcitonin in serum and significantly lower concentrations of calcium in urine than did 23 normal pregnant controls. The differences were most pronounced in the third trimester. The results obtained in the low-dose heparin group were between those in the high-dose and the control groups. At 8 weeks postpartum there were no significant differences between the heparin-treated women and the controls. No significant differences were found during pregnancy in haematocrit, liver or renal function, serum levels of albumin, phosphate, magnesium, alkaline phosphatase, parathyroid hormone or urinary cyclic AMP.

Conclusions Heparin treatment during pregnancy results in changes in calcium homeostasis and a dose-dependent response is suggested.

The risk of thromboembolism is considerably increased during pregnancy (Aaro & Juergens 1971; Bonnar 1987). Previous history of thromboembolism further increases the risk (Badaracco & Vessey 1974; Tengborn *et al.* 1989) and is usually regarded as an indication for thromboprophylaxis in later pregnancy (de Swiet *et al.* 1980, Bonnar 1987).

Warfarin and other oral anticoagulants are usually avoided because of adverse maternal and fetal effects (Ginsberg & Hirsh 1989). Heparin is often used as it does not affect the fetus (Ginsberg & Hirsh 1989). Currently, thromboprophylaxis during pregnancy is the main indication for long-term heparin treatment. However, long-term heparin treatment has been associated with osteoporosis (Griffith *et al*; 1965, Avioli 1975) and several case reports have described multiple vertebral fractures after such a regimen during pregnancy (Squires & Pinch 1979; Aarskog *et al* 1980; Wise & Hall 1980; Megard *et al.* 1982; Hellgren & Nygårds 1982; Griffiths & Liu 1984; Zimran *et al.* 1986; Dahlman *et al.* 1990).

During normal pregnancy, calcium homeostasis changes and adapts to maintain ionized calcium within the normal range, mainly by increasing intestinal absorption (Pitkin 1985). Protection of the maternal skeleton from excessive resorption may be caused by the increase in calcitonin reported during normal pregnancy (Stevenson *et al.* 1979). The changes in calcium homeostasis that may be induced by heparin have not been studied prospectively during pregnancy.

In the present study, calcium homeostasis was studied longitudinally in pregnant and puerperial women during high- and low-dose heparin regimens, and in a control group of healthy pregnant women.

Subjects and methods

The study involved 36 pregnant women with a history of verified thromboembolic complications, who had been referred to the Karolinska Hospital for prophylactic heparin treatment. Samples of venous blood and urine were taken before heparin was started and thereafter every 4 weeks between 14 and 38 weeks gestation and again at 5 days and 8 weeks after delivery. In addition, 23 healthy pregnant women without medication

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Table 1. Characteristics of the women in the study

	Heparin groups		
	High-dose (n = 16)	Low-dose (n = 20)	Controls (n = 23)
Age (years) mean (SD)	31 4 (6·0)	29·6 (5·8)	27·7 (4·9)
Weight (kg) mean (SD)	60·9 (6 1)	60·7 (4·1)	58 6 (5·6)
Nulliparae (%)	43·8	40 0	52·2
Smokers (%)	37 5	40·0	30 4

were followed in the same way and served as controls. The women in both groups had normal pregnancies, uneventful deliveries and a normal puerperium. There were no significant differences between the heparin-treated and control women with respect to age, parity, weight, and smoking habits (Table 1). Oral contraceptive pills were not used in the puerperium and all women breast-fed their children. No calcium supplements were given.

All women gave their informed consent to the study which was approved by the ethics committee at Karolinska Hospital.

Heparin treatment

Unfractionated standard sodium heparin (Heparin, Kabi-Pharmacia AB, Stockholm, Sweden) was injected subcutaneously twice daily by the women. The mean time for starting the treatment was in the 13th week (range 6–30 weeks) and it was discontinued in the 6th week postpartum (2 weeks before the last sampling).

The women were recruited consecutively and all, regardless of indication, were given the same dose of heparin when entering the study (7500 IU twice daily). The dose was adjusted according to the heparin effect which was monitored using one method at the beginning of the study and another method in the later part of the study. After completion of the study, the second method for monitoring the heparin effect proved to have been more sensitive so that these women had been given less heparin. A high- and a low-dose heparin group were thus created fortuitously. During the two periods of time, when the two treatment groups were formed, the selection of patients was the same and the two heparin groups were similar regarding so called high- and low-risk patients.

The first group, consisting of 16 women (high-dose heparin regimen), was monitored by checking the activated partial thromboplastin time (APTT) 3 h after the injection and with the dose adjusted to provide a prolongation of 10–15 s. The mean dose of heparin was 24 500 IU/day (SD 5500). The mean duration of treatment during pregnancy was 22·5 weeks (range 9–33 weeks).

The second, later group consisting of 20 women (low-dose heparin regimen), was monitored by checking the plasma heparin concentration 3 h after injection. The dose was adjusted to achieve an anti-factor Xa-activity corresponding to a heparin concentration of 0·08–0·15 IU/ml (Dahlman *et al.* 1989). The mean dose of heparin in this group was 17 300 IU/day (SD 3100). The mean duration of treatment during pregnancy was 23·3 weeks (range 6–32 weeks).

Postpartum both groups were given 15 000 IU of heparin/day.

Methods

Venous blood samples were obtained at 0800 hours after a 12 hour fast and the haematocrit was determined. Serum was analysed by routine photometric methods for total calcium, magnesium, phosphate, albumin and alkaline phosphatase. Samples for ionized calcium were analysed within an hour with a calcium flow-through electrode, ORION SS-20 (ORION Biomedical Inc., Cambridge, MA, USA; reference range 1·14–1·27 mmol/l).

Serum frozen at minus 70°C was later analysed for parathyroid hormone (PTH) and calcitonin. PTH was determined by radioimmunoassay using antibodies directed against the midportion of the peptide (PTH OMEGA fragment 53–68, Cambridge Medical Diagnostic Inc., Cambridge, MA, USA). The reference range was 0·5–1·5 μg/l and the lower limit of detection was 0·17 μg/l. Calcitonin was analysed by radioimmunoassay using antibodies directed against the C-terminal fragment. The reference range for non-pregnant women was <8–19 pg/ml (median 9 pg/ml) when undetectable levels were assigned the value of the detection limit (8 pg/ml) (Bucht *et al.* 1985). Intra- and interassay variations were 10% and 16%, respectively. Urine was collected over a 24-h period. Calcium and creatinine were analysed by routine photometric methods and cyclic AMP by a protein-binding assay method (Geissler *et al.* 1977). All analyses were made in duplicate.

Statistical analysis

Changes during pregnancy and differences between groups were analysed by Kruskal Wallis one-way analysis of variance.

Results

The mean values and SD for total and ionized calcium and calcitonin in serum, and for calcium in urine in the two treatment groups and controls, are given in Table 2. Significant differences during pregnancy (by analysis of variance) were found between the high-dose heparin treatment group and the control group. All groups started with comparable concentrations in the 14th week of gestation, the differences being most pronounced at the end of pregnancy. The results obtained in the low-dose heparin group were between those in the high-dose heparin group and the control group.

As illustrated in Fig. 1a the serum total calcium concentration remained at about the same level during pregnancy in the high- and the low-dose heparin groups. Significantly higher levels of total calcium were found in the high-dose heparin group than in the controls ($P<0{\cdot}01$). After delivery, the values increased significantly in all groups and were almost identical 8 weeks postpartum. The serum levels of ionized calcium were significantly higher in the high dose heparin group than those in the controls during pregnancy ($P<0{\cdot}001$) (Fig. 1b). The serum levels of calcitonin (Fig. 1c) were increased during pregnancy in the high-dose heparin group and significantly different from those in the controls ($P<0{\cdot}01$). The differences were most pronounced at the end of pregnancy. The urinary excretion of calcium (Fig. 1d) showed a gradual decrease during pregnancy in the high-dose heparin group ($P<0{\cdot}01$) which differed significantly from that in the controls ($P<0{\cdot}05$). In contrast, similar serum levels of PTH,

Table 2. Serum concentrations of total calcium, ionized calcium and calcitonin and urinary calcium in heparin high-dose ($n = 16$), heparin low-dose ($n = 20$) and control groups ($n = 23$) followed longitudinally during pregnancy and the puerperium

	Week of pregnancy							Week postpartum	
Group	14	18	22	26	30	34	38	1	8
Serum total calcium (mmol/l)									
High-dose	2·30	2·31	2·29	2·25	2·27	2·28	2·27	2·27	2·38
	(0·08)	(0·12)	(0·13)	(0·15)	(0·12)	(0·09)	(0·13)	(0·12)	(0·15)
Low-dose	2·26	2·21	2·24	2·21	2·22	2·19	2·24	2·30	2·37
	(0·12)	(0·08)	(0·10)	(0·09)	(0·11)	(0·10)	(0·13)	(0·13)	(0·10)
Control	2·31	2·21	2·23	2·16	2·16	2·15	2·14	2·18	2·37
	(0·15)	(0·11)	(0·16)	(0·15)	(0·12)	(0·12)	(0·11)	(0·15)	(0·13)
Non-pregnant reference range = 2·20–2·60 mmol/l									
Serum ionized calcium (mmol/l)									
High-dose	1·23	1·23	1·23	1·25	1·23	1·24	1·22	1·27	1·23
	(0·01)	(0·05)	(0·06)	(0·06)	(0·07)	(0·04)	(0·07)	(0·08)	(0·04)
Low-dose	1·20	1·21	1·21	1·20	1·21	1·22	1·21	1·24	1·25
	(0·04)	(0·04)	(0·06)	(0·05)	(0·08)	(0·07)	(0·04)	(0·07)	(0·05)
Control	1·20	1·19	1·20	1·20	1·18	1·17	1·19	1·22	1·24
	(0·05)	(0·06)	(0·05)	(0·05)	(0·04)	(0·06)	(0·05)	(0·06)	(0·04)
Non-pregnant reference range = 1·14–1·27 mmol/l									
Serum calcitonin (pg/ml)									
High-dose	25 (10)	32 (18)	33 (17)	33 (18)	30 (17)	34 (18)	38 (20)	31 (17)	26 (19)
Low-dose	25 (24)	24 (24)	25 (23)	23 (23)	25 (23)	27 (20)	27 (21)	23 (21)	22 (23)
Control	20 (12)	18 (12)	19 (11)	19 (12)	21 (12)	21 (15)	20 (12)	20 (12)	17 (11)
Non-pregnant reference range = <8–19 pg/ml									
Urinary calcium (mmol/24h)									
High-dose	5·3	6·3	5·0	5·2	4·9	4·8	2·8	2·6	1·9
	(1·8)	(2·0)	(2·7)	(2·2)	(1·6)	(2·4)	(1·3)	(1·4)	(1·1)
Low-dose	7·1	6·7	6·1	5·3	6·9	5·9	4·9	3·9	2·7
	(3·7)	(4·2)	(3·6)	(3·0)	(5·0)	(4·5)	(3·2)	(2·6)	(1·1)
Control	6·4	6·7	6·4	6·4	6·9	7·6	6·5	3·6	2·5
	(2·5)	(2·5)	(2·5)	(2·3)	(4·1)	(3·2)	(3·1)	(2·6)	(2·0)
Non-pregnant reference range = 1·0–7·0 mmol/24h									

Results are mean (SD) values.

albumin, magnesium, phosphate, alkaline phosphatase and creatinine were present in all three groups. The haemoglobin, haematocrit, hepatic enzymes as well as urine values of creatinine and cyclic AMP showed no significant differences.

Discussion

During normal pregnancy the fetal demand for calcium may impose an increased demand on the maternal skeleton and result in bone loss (Lamke *et al.* 1977). Some case reports describing osteoporosis with hip or vetebral fractures in normal pregnancy have also been published (Smith *et al.* 1985). However, in another study, normal pregnancy was not associated with maternal bone loss (Christiansen *et al.* 1976).

The first case report describing heparin-induced osteoporosis with spinal fractures was published by Griffith *et al.* (1965) who described a dose-dependent relation. During the last decade, most case reports on this subject have been connected with pregnancy (Squires & Pinch 1979, Aarskog *et al.* 1980; Wise & Hall 1980; Megard *et al.* 1982; Hellgren & Nygårds 1982; Griffiths & Liu 1984; Zimran *et al.* 1986; Dahlman *et al.* 1990).

After long-term heparin treatment radiological signs of postpartum osteopenia have been noted in 17% of women (Dahlman *et al.* 1990). Similarly, women having heparin prophylaxis during pregnancy are reported to have decreased phalangeal cortical thickness and this appears to vary with the duration of treatment (deSwiet *et al.* 1983). Not only human but also animal experiments support the relation between heparin and osteoporosis (Avioli 1975; Ambrus *et al.* 1978; Mätzsch *et al.* 1986). The latter report showed a dose-dependent relation. Furthermore, mastocytosis with an increased number of heparin-containing mast cells is often accompanied by osteopenia and vertebral fractures (Fallon *et al.* 1981) and increased numbers of mast cells have been found in women with postmenopausal osteoporosis (Fallon *et al.* 1983). Disturbed haemostasis with significant prolongation of APTT as well as systemic heparin activity has also been seen in patients with mastocytosis (Campbell *et al.* 1979).

The mechanism by which heparin causes osteoporosis is not known but several theories have been proposed (Avioli 1975). A decrease in the amount of bone collagen synthesis (Thompson 1973), and an increase in the collagenase activity (Starcher *et al.* 1980) have been reported.

The physiological response may be a reduction in the urinary excretion of calcium. Increased levels of calcitonin may

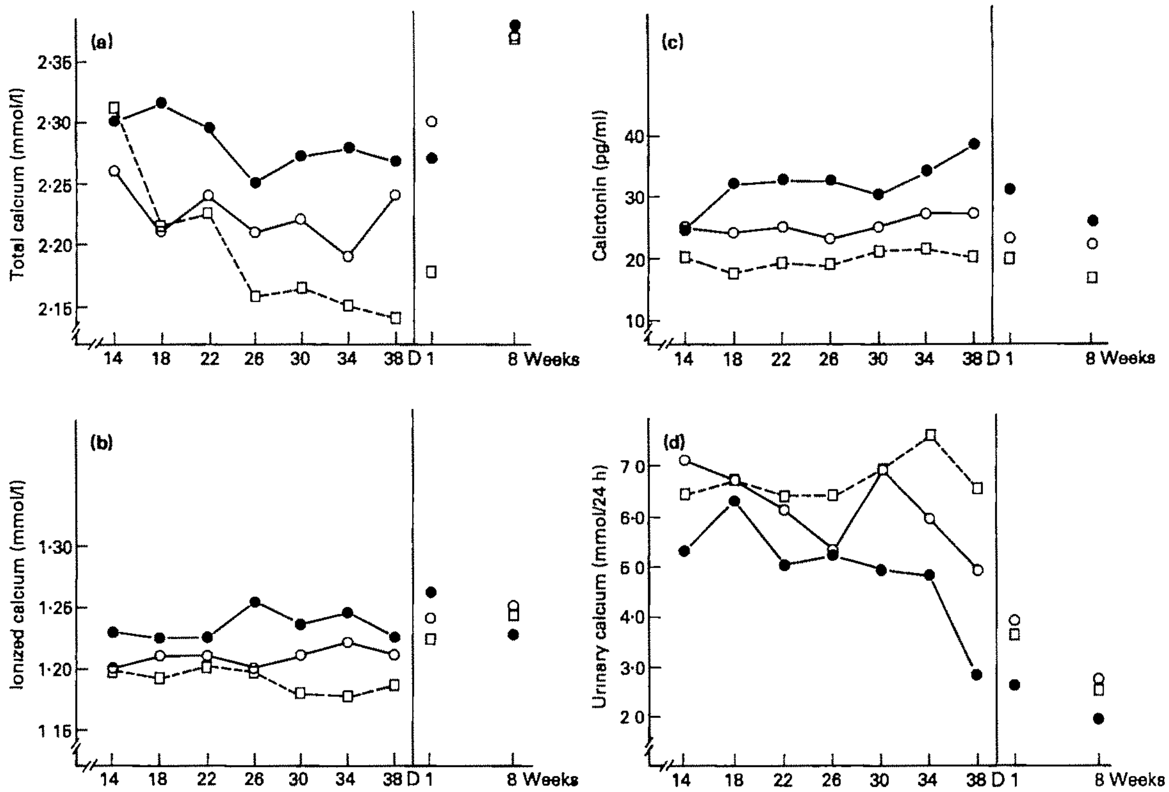

Fig. 1. Changes in calcium homeostasis during pregnancy and the puerperium in high-dose (●—●) and low-dose (○—○) heparin regimens, compared with controls (□—□). D = delivery. (a) Serum total calcium, (b) serum ionized calcium, (c) serum calcitonin, (d) urinary calcium excretion.

also play a protective role (Stevenson *et al.* 1979). Our results indicate that both of these mechanisms act during heparin treatment. Particularly in the high-dose heparin group, urinary calcium excretion gradually decreased and serum calcitonin steadily increased. Perhaps, in consequence of a renal conserving mechanism, the total and ionized calcium levels in serum during heparin treatment were maintained within the normal range throughout pregnancy in contrast to the control group where the serum total calcium level gradually decreased and the fall paralleled that of the serum albumin level. However, no differences in serum albumin were seen between the control and the heparin groups.

It has been shown previously that serum levels of calcitonin are consistently elevated throughout normal pregnancy (Stevenson *et al.* 1979), and during heparin treatment a further increase was observed by us. The physiological stimulator of calcitonin is an increased serum ionized calcium level. The latter was significantly increased during the high-dose heparin treatment, and the increase was dependent on the amount of heparin administered. This increase in ionized calcium can be explained by either the decrease in renal calcium excretion, or by the enhanced osteoclastic activity following heparin administration. Some data indicate that heparin exerts its effect on bone by acting as a co-factor of PTH (Goldhaber 1965) or by secondary hyperparathyroidism (Avioli 1975). We found no evidence of increased PTH activity or urinary cyclic AMP during heparin treatment, which indicates that, if osteolysis occurs, it is more likely to be caused by a direct effect of heparin on bone than via PTH. However, the PTH method used in our study may be too insensitive to measure the biologically active form. Another theoretical explanation of heparin-mediated osteolysis that could clarify our findings is a PTH-like effect of PTH related peptide (PTHrP) (Editorial 1991) triggered by heparin. The PTH-like effect with decreased urinary calcium excretion and bone resorption would also result in an increased ionized calcium in serum and a secondary increase in calcitonin.

Our data indicate that the higher the dose of heparin, the greater is the challenge to maternal calcium homeostasis. In the postpartum period and after the discontinuation of treatment, calcium homeostasis rapidly returned to normal. Furthermore, heparin-induced osteopenia seems to be reversible (Dahlman *et al.* 1990) but decreased bone density 2 years after treatment is also reported (Ginsberg *et al.* 1990).

Those pregnant women who develop severe osteoporosis with fractures during heparin treatment may be unable to protect themselves by a sufficient increase in calcitonin or by a decrease in renal calcium excretion. The question whether supplemental calcium, calcitonin and/or calcitriol might be beneficial should be examined.

Osteoporosis must be taken into account when considering prophylactic heparin treatment during pregnancy. When heparin is administered it is advisable to give the lowest effective dose. Monitoring the anticoagulant effect of heparin, preferably as anti-factor Xa activity, is recommended (Dahlman *et al.* 1989). Some authors have proposed limited use during pregnancy (Letsky & de Swiet 1984) but it should not be discontinued altogether in high-risk patients, since this would undoubtedly increase the risk of deep vein thrombosis and fatal pulmonary embolism.

Acknowledgments

This study was supported by the Swedish Medical Research Council (grant no. 5992), King Gustaf V's and Queen Victoria's Research Foundations, as well as Claes Groschinsky's Memorial Foundation. We are also grateful to Astrid Häggblad for preparing the manuscript and to Marita Johansson for drawing the figures.

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Received 9 July 1991
Accepted 28 November 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 417–421

REPRODUCTIVE SCIENCE

Vaginosonographic velocimetry in uterine arteries before and after administration of beta-mimetics

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ABSTRACT

Objective To investigate the effect of surgical procedures at 15 weeks gestation (amniocentesis or cervical cerclage), with or without post-operative ritodrine prophylaxis, on uterine blood flow velocity waveforms and maternal heart rate.

Design A quasi-randomized observational study.

Setting University Department of Obstetrics and Gynaecology, Vienna.

Subjects Sixty women having a genetic amniocentesis for advanced maternal age and 57 women having elective cervical cerclage for previous preterm labour or recurrent miscarriage.

Interventions The women in each group were allocated either to receive prophylactic ritodrine postoperatively or to receive no ritodrine treatment. Allocation used the year of birth of the woman (odd years received ritodrine, even years received no treatment). All the women had vaginal ultrasound velocimetry studies in both mainstem uterine arteries through the parametrium before the surgical procedure and again after the procedure. The ritodrine-treated women in the cerclage group received intraveneous ritodrine hydrochloride (0·2 mg/min) and those in the amniocentesis group received 60 mg ritodrine/day orally.

Main outcome measures Uterine artery blood flow velocity waveform indices: A/B ratio and pulsatility index (PI) and maternal heart rate before and after the surgical procedure.

Results The only statistically significant difference in haemodynamic values between those obtained before the procedure and those obtained after the procedure with or without prophylactic ritodrine was seen in the women who had cervical cerclage with postoperative intravenous ritodrine. The mean A/B ratio decreased from 2·69 (SD 1·17) to 2·11 (SD 0·44), and the mean PI from 1·62 (SD 0·47) to 1·21 (SD 0·3) and the mean maternal heart rate increased from 82·6 (SD 11·1) to 99·4 (SD 15·7). There were no other statistically significant differences between before and after haemodynamic values.

Conclusions There are no clinically relevant effects of amniocentesis and cervical cerclage on uterine blood flow velocity waveforms.

Ritodrine, a beta-adrenergic receptor agonist, is often prescribed for inhibition of preterm labour and is also administered after cervical cerclage to prevent the possible initiation of uterine contractions. The same consideration arises with genetic amniocentesis although physicians vary widely in opinion about the benefits of ritodrine in this situation. The pharmocokinetics of ritodrine have been extensively studied in animals and humans. Maternal cardiovascular effects have received much attention (Wilkins *et al.* 1988), because the administration of beta-mimetics can be associated with undesirable cardiovascular and metabolic side effects (Benedetti 1983; Ferguson *et al.* 1989). In the therapeutic range maternal effects include an increase in heart rate, widening of the pulse pressure and a slight increase in cardiac output (Vojcek & Lampe 1985). The drug causes relaxation of the uterine smooth muscle and therefore may also affect uterine blood flow. However, studies on uterine blood flow in human are few and have not shown consistent results. Likewise, a correlation between surgical procedures (cervical cerclage or amniocentesis), subsequent contractions and their effect on uterine blood velocity wave forms have not been investigated. This stimulated our interest to study uterine artery blood flow velocity waveforms using vaginal Doppler ultrasound.

The aim of the study was to investigate changes in uterine blood flow velocity wave forms after amniocentesis or cervical surgery with or without prophylactic ritodrine.

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Subjects and methods

The study included 117 women with a singleton pregnancy between 14 and 16 weeks gestation. All had accurate pregnancy dating by early ultrasound measurements. None of the women studied had taken any medication at the time of first testing except for vitamins or iron supplementation or both. All the women in the study had given informed consent and the study design was approved by our ethics committee. None of the women included in the study had hypertension, cardiac disease, diabetes mellitus, endocrine disorders, drug or alcohol abuse or a haematocrit <25%.

Sixty of the women were undergoing genetic amniocentesis for maternal age >35 years or a combined parental age >70 years. The other 57 were undergoing prophylactic cervical cerclage because they had had a previous preterm delivery or two or more miscarriages with subsequent curettage. The women in the amniocentesis group were allocated either to receive postoperative beta-mimetics (ritodrine hydrochloride, Prepar, Duphar, Kali-Chemie Pharma, Vienna, Austria) or not to receive ritodrine. Allocation was based on the woman's year of birth, an odd year of birth put her into the ritodrine group ($n = 30$) and an even year into the no treatment group ($n = 30$). In the same way the women in the cerclage group were allocated to receive postoperative ritodrine treatment ($n = 29$) or to receive no treatment ($n = 28$). No placebo was administered.

Table 1 gives the characteristics of the four groups in the study. None of the women in the cerclage groups showed signs of uterine contractions like cramping or effacement of the cervix at the time of the procedure.

Protocol

All the women had Doppler velocimetry studies preoperatively (cerclage or amniocentesis) and these studies were repeated the day after the procedure in the amniocentesis groups and 6 h after the procedure (late in the afternoon of the same day) in the cerclage groups. In the treatment groups, women having an amniocentesis received ritodrine hydrochloride 10 mg orally every 4 h, which amounted to a daily dosage of 60 mg. At the initiation of the study we thought that this would result in an adequate maternal ritodrine level and it was the usual dosage.

Women undergoing cervical cerclage were admitted to hospital and treated with intravenous ritodrine hydrochloride (0·2 mg/min) and bed rest for 24 h immediately after the procedure. They were placed on the oral regimen later. Thereafter, moderate physical activity was allowed.

Doppler studies

Using a vaginal Duplex scanner (Kretztechnik Corp., Zipf, Austria) we were able to scan the parametrium on both sides and identify echos of the uterine arteries (Fig. 1). The Doppler beam vector and the gate were positioned in the pulsating vessel. Switching from the real time mode to the Doppler mode we received the frequency shift according to the velocity of the erythrocytes in that vessel. Mean values for total uterine velocity waveform could be calculated from left and right indices because measurements were performed in both uterine arteries. We could obtain satisfactory signals in all women investigated. In some cases we needed a second attempt because the patients' bladder was not quite empty and orientation was difficult. Further technical details concerning the apparatus and the method of vaginsosonographic Doppler velocimetry have been published previously (Deutinger *et al* 1988).

Table 1. Demographic data of the women in the study

	Amniocentesis group		Cervical cerclage group	
	Ritodrine	No treatment	Ritodrine	No treatment
Age (years)	($n = 30$)	($n = 30$)	($n = 29$)	($n = 28$)
Mean (SD)	38·2 (2·4)	37·8 (2·3)	25·1 (2·9)	26·4 (2·5)
Nulliparae	4	6	10	9
Multiparae	26	24	19	19

Data analysis

Analysis of the waveforms included calculation of the A/B ratio (A = maximum frequency shift during systole, B = maximum frequency shift during diastole), the pulsatility index (PI, maximum frequency shift during systole minus least frequency shift during diastole divided by the mean frequency shift during diastole) (Gosling & King 1975) and maternal heart rate. A built-in computer program calculates these values after the waveforms have been outlined, either automatically or manually by means of a light pen. Measurements were taken from 3 to 4 waveforms and averaged. The mean (SD) values always represent an average of the right and left uterine arteries.

For statistical evaluation we used the paired *t*-test. Significant levels were assumed when $P<0{\cdot}05$.

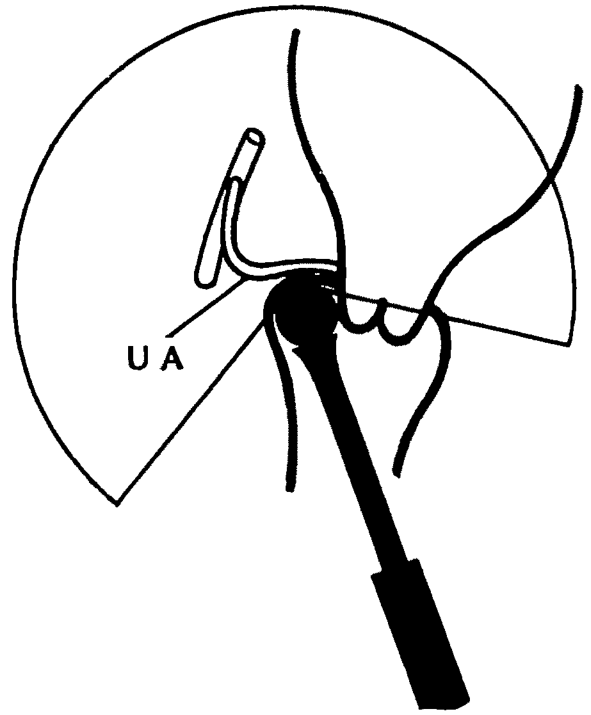

Fig. 1. Vaginosonographic blood flow velocimetry in the right uterine artery. The drawing provides a schematic view of the transducer's position in the right lateral fornix of the vagina and the main uterine artery on its course through the parametrium: UA = uterine artery.

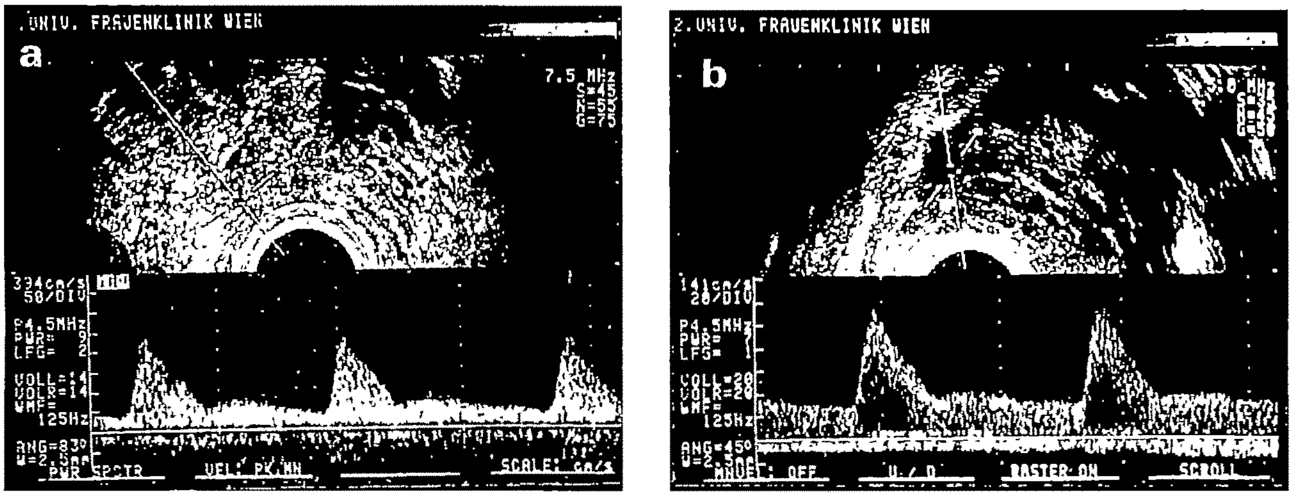

Fig. 2. Vaginosonographic Doppler blood flow velocimetry in the right uterine artery at 15 weeks gestation before cervical cerclage (a) and after cerclage and intravenous ritodrine (b). Note the increase in the diastolic blood flow velocity.

Results

From the 117 women, undergoing studies on the right and left uterine artery on two occasions each, we obtained 468 measurements. Figure 2 shows the velocity waveforms of the right main uterine artery in a women before and after cerclage at 15 weeks gestation and intravenously administered ritodrine hydrochloride. Only in this group (cervical cerclage with postoperative ritodrine) could we observe a significant difference in haemodynamic values between before and after the procedure; the mean A/B ratio decreased from 2·69 (SD 1·17) to 2·11 (SD 0·44) and the mean PI from 1·62 (SD 0·47) to 1·21 (SD 0·3) the mean maternal heart rate increased from 82·6 (SD 11·1) to 99·4 (SD 15·7). None of the other three groups studied (cerclage without ritodrine and amniocentesis with or without ritodrine) showed any statistically significant difference between values obtained before and after the procedure (Table 2).

Discussion

There are few reports describing second trimester uterine haemodynamics. The possible influence of surgical procedures and drug effects has not been investigated due to the lack of appropriate noninvasive methods. Invasive measurements in pregnant sheep suggested a reduction in uterine perfusion during ritodrine infusion (Kleinman *et al.* 1984).

Main stem uterine artery measurements

Most clinical investigations of uterine blood flow velocity have used the transabdominal technique. Their main interest focused on the effect of tocolysis. Brar *et al.* (1988) reported a decrease in the A/B ratio in 'uterine arteries' when ritodrine was administered intravenously in increasing dosages. Since they studied women in preterm labour around 36 weeks gestation, a possible effect of uterine tension or contractions or both cannot be excluded. It is noteworthy that neither magnesium sulphate (Brar *et al.* 1988) nor nifedipine (Mari *et al.* 1989) were found to affect uterine blood flow velocity waveforms.

This is the first reported study of the influence of betamimetics, cervical cerclage and genetic amniocentesis on uterine velocity waveforms in the second trimester. We would like to emphasize that transabdominal Doppler velocimetry is possible only in branches of the uterine artery and the chance to measure in the mainstream uterine artery is only as high as 30% (Fendel & Sohn 1989). Therefore, transabdominal ultrasound measurements are performed in the arcuate arteries, which are often not visible even by means of high-resolution

Table 2. Mainstem uterine artery (left and right) blood flow velocity waveform indices before and after amniocentesis or cervical cerclage with or without postoperative ritodrine prophylaxis

Haemodynamic indices	Amniocentesis group				Cerclage group			
	Ritodrine (*n* = 30)		No ritodrine (*n* = 30)		Ritodrine (*n* = 29)		No ritodrine (*n* = 28)	
	Before	After	Before	After	Before	After	Before	After
AB ratio	2·67 (0·90)	2·54 (0·86)	2·63 (0·70)	2·66 (0·76)	2·69 (1·17)	2·11 (0·44)*	2·62 (1·14)	2·61 (0·76)
PI	1·67 (0·46)	1·58 (0·75)	1·53 (0·44)	1·54 (0·40)	1·62 (0·47)	1·22 (0·30)*	1·54 (0·46)	1·50 (0·48)
MRH	81·4 (11·4)	89·7 (18·5)	85·3 (11·6)	90·2 (13·2)	82·6 (11·1)	99·4 (15·7)*	84·0 (12·6)	83·9 (15·9)

*Significance of difference between before and after the procedure and ritodrine administration, $P<0·05$.

PI = pulsatility index; MHR = maternal heart rate.

Results are mean (SD) values.

ultrasound equipment and are only terminal branches of the uterine arteries. Moreover, the continuous wave technique can recognize vessels only by their typical waveforms (when normal). It is not surprising, that the reproducibility of this technique has been poor (Neilson 1987). Nevertheless, and as technology advances, we expect that colour Doppler flow mapping will be most helpful in improving the situation.

Using a vaginal Duplex scanner, we were able to perform velocimetry on both mainstrem uterine arteries which provide a good summary of uterine haemodynamics. This is especially important in this early stage of gestation, because high left-right differences have been reported in early pregnancy and unilateral measurement may give erroneus results (Schulman *et al* 1987; Deutinger *et al.* 1988, 1991). Schulman *et al.* (1986) reported similar A/B ratios for bilateral and vaginal measurements at 16 weeks gestation using a continuous wave-Doppler ultrasound.

Reasons for a decrease in the A/B ratio

Our results agree with the observations of Brar *et al.* (1988), we found a significant decrease in the haemodynamics indices after intravenous ritodrine in the second trimester. The change in uterine blood flow velocity seems to be caused by several effects. One is the effect on the heart. The positive inotropic and chronotropic action of ritodrine increases the cardiac output. The other effect is on the general vasculature. Vasodilatation and particularly the dilatation of the uterine vascular bed accounts for a greater portion of cardiac output to be shunted toward the uterus. However, it is difficult to determine which effect is the most important, chronotropy, inotropy or vasodilatation. It is well known that alteration in maternal heart rate influences the A/B ratio as well as the PI, for instance there is a negative correlation between fetal heart rate and the umbilical artery A/B ratio (Fairlie & Lang 1988). We also observed this phenomenon in the women treated with ritodrine after cervical cerclage, their heart rate increased from 83 to 89 and both the A/B ratio and PI decreased significantly. However, the PI is calculated from the mean velocity during a cardiac cycle. Thus, the influence of elevated end-diastolic blood flow velocity due to increased heart rate is minimized so we can assume that the vasodilatory effect on the uterine arteries contributes more to this decrease than chronotropy. Another effort in pinpointing the effect of chronotropy could be made by a correction of the waveforms for increased heart rate. Kofinas *et al.* (1989) found it not necessary to do so, since only 13% of the variability in the AB ratio can be attributed to changes in the heart rate. But as mentioned before, a small effect must be credited to the positive chronotropic effect as well.

Effect of oral ritodrine on uterine haemodynamics

Oral ritodrine was reserved primarily for outpatient treatment. Since it was our current clinical regimen then, we prescribed 10 mg ritodrine every 4 h. We are aware of reports in the literature stating that it requires more frequent administration and higher dosages in order to achieve and sustain tocolytic blood levels of ritodrine (Gandar *et al.* 1980). However, the maximum recommended dose of the oral ritodrine preparation is 20 mg every 4 h (Witter *et al.* 1988). This might explain our finding that oral ritodrine had no significant effect on the waveform in uterine arteries. This is supported by the fact that oral ritodrine did not raise maternal heart rate significantly. Another reason could be that our equipment is not sensitive enough to recognize a measureable effect.

Amniocentesis and cerclage operation did not affect blood flow velocity in the mainstem uterine arteries. During cervical cerclage only a branch of the descending uterine artery might be ligated, but this seems not to influence the blood flow velocity in the mainstem uterine artery. Vaginal pulsed Doppler velocimetry in both mainstem uterine arteries showed that intravenously administered ritodrine led to a decrease of the A/B ratios and the PIs. Neither orally administered ritodrine nor cerclage operation nor genetic amniocentesis affected uterine blood flow velocity.

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Received 11 July 1991
Accepted 19 December 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 422–429

REPRODUCTIVE SCIENCE

Length and variation in the menstrual cycle—a cross-sectional study from a Danish county

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ABSTRACT

Objective To investigate the current epidemiology of menstrual patterns among women of fertile age.
Design Cross-sectional postal questionnaire study.
Setting County of Copenhagen, Denmark.
Subjects 3743 women, aged 15–44, selected at random from a Danish county, who were asked to provide information on menstrual pattern during the preceding year, 1981. The response rate was 78%. Information from non-responders was obtained via telephone interviews.
Results In women with regular menstrual cycles, the 5th–95th centile range of usual cycle length decreased from 23–35 days in the 15–19 years age group to 23–30 days in the 40–44 years age group. Only 0·5% of regular menstruating women had a usual cycle length of <21 days and 0·9% had a usual cycle length of >35 days. At least one cycle length of <21 days was experienced by 18·6%, whereas 29·5% had at least one cycle of >35 days. Menstrual cycle variation of >14 days was present in 29·3% of all women. Cycle length variation of >14 days was 2·7 times more frequent in women from lower social groups (controlled by age).
Conclusion The study confirmed the normally used definitions of polymenorrhoea (cycle length <21 days) and oligomenorrhoea (cycle length between 36 and 90 days), as these very short or long menstrual cycle lengths were very seldom recorded for a longer period. However, the high frequency in a normal population of large menstrual cycle length variation challenges the view that an intra-individual variation of >5 days should be regarded as a sign of disease in the woman.

Knowledge of the length and variation of the menstrual cycle is necessary for the assessment of menstrual irregularities and these variables have been examined in large prospective studies with pooling of data from women over a period of more than 30 years (Treolar *et al.* 1967; Vollman 1977). More recently, large cross-sectional studies have been made by Chiazze *et al.* (1968) and by the WHO Task Force on Methods for the Determination of the Fertile Period (1983). In all these studies, the women were more or less highly selected (college women, patients in general practice, even women involved in a study of 'natural' contraceptive methods that demanded that the women had regular cycles). In the longitudinal studies, a considerable percentage of women, for unspecified reasons, did not participate in follow up. Thus, the degree to which these women's menstrual patterns were representative for all women in the population is uncertain.

Moreover, changes in contraceptive use and the smaller number of births in the past 15 to 20 years may have influenced menstrual patterns. The present study was undertaken to investigate the current epidemiology of menstrual patterns among women of fertile age in a large Danish county over a defined time period.

Subjects and methods

The study population comprised 3743 women, aged 15–44 years. All were Danish citizens, residing in the County of Copenhagen. The county's total female population in this age group was 136 148. From a list of random numbers, a 2·75% sample was drawn of all birth dates between 1 January 1944 and 31 December 1973. This percentage was chosen to ensure a sample of at least 3500 women. From the National Central Person Register, we obtained information on the name, residence, and occupation of all women born on these dates. The women received a postal questionnaire in spring 1989. A total of up to three letters (including the questionnaire) was sent. The women were further requested to send their menstrual calendar record for 1988 (Danish school health education emphasizes the value of keeping such a calendar). A search was made for the addresses of women who had moved, through the post office and municipal registration bureaux. Sixty women were excluded from the study, these were women who had emigrated permanently; those with temporary residence in foreign countries for more than 5 months; those who could not be traced; and those who were intellectually ill-equipped to fill in the questionnaire.

There were 2865 responders, a response rate of 78% (four responders did not complete the questionnaire and were

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excluded). Responders and all non-responders were compared for age, municipality, and occupation, although the occupational data for non-responders was not very precise as it had not been updated accurately by the National Central Person Register. From non-responders, a 27·3% sample was drawn by lots and when possible, the women were contacted by telephone for a short, structured interview. On ethical grounds, non-responders who stated they did not want to contribute to the study ($n = 88$) were excluded when lots were drawn for the interview group.

In the analyses of the menstrual patterns for 1988, women were excluded if they had had a hysterectomy or bilateral oophorectomy, were premenarcheal, were using oral contraceptives in 1988, and if they had been pregnant, had given birth, or had lactated in 1988. The frequency of exclusions by age is illustrated in Table 1. Subsequently, 1526 women remained for the analyses.

Statistical methods

Data were processed using the standard computer programs SPSS (Norusis 1988) and Medstat (Wulff & Schlichting 1988). Centiles and frequencies were preferred in most analyses, since most of the results were not normally distributed, and these measures retain the original distribution of results. Arithmetic mean and standard deviation were used in one analysis to allow a comparison with other studies. Linear regression was used in the analysis of usual length of the menstrual cycle by age. In the analyses of non-responders, direct age standardization was used in description of frequencies, and the Mantel-Haenszels test was used for testing of hypotheses, as a number of variables were highly age dependent. Other variables were analysed by means of the χ^2 test (with Yates' correction when appropriate) or with Fisher's exact test for the 2 × 2 table.

Definitions

Length of menstrual cycle. This was defined as the interval (in days) from the first day of one menstruation to the first day of the next menstruation. For women from whom we received a complete and valid menstrual calendar record, the values from the calendar record were used.

Usual menstrual cycle length during 1988. Four alternative answers were available to this question. (i) Stated length in days. (ii) Totally irregular cycles, without any fixed time patterns. (iii) Menstrual cycles not yet begun. (iv) No menstrual cycles in 1988. Usual cycle length was only analysed in women who belonged to the first category ($n = 1301$).

Intra-individual variation in 1988. The following variables were used. (i) Length of the shortest menstrual cycle in 1988 (days). (ii) Length of the longest menstrual cycle in 1988 (days). (iii) Maximum menstrual cycle variation in 1988, calculated as the difference betwen the longest and the shortest menstrual cycle in 1988 (days). These values were analysed separately for the women with a usual regular menstrual cycle and for all menstruating women ($n = 1493$).

Comparisons were made between the women with a complete and valid menstrual calendar record ($n = 620$), women who stated that they kept a menstrual calendar record but had already discarded it ($n = 289$), and women who had not kept any menstrual calendar record ($n = 617$).

Coding of menstrual calendar records

In the calendar group, the following predetermined rules for the coding of data, undertaken by one of the authors (K.M.), were used: If a bleeding episode was separated from the next bleeding episode by >3 days without bleeding, the subsequent bleeding episode was counted as the beginning of a new menstrual cycle. In fact, the shortest registered cycle was 7 days.

If a bleeding episode lasted for only 1 day and the woman had stated that her bleeding episodes were longer than one day, the bleeding episode was interpreted as spotting.

Usual menstrual cycle length was defined as the median value of the year's menstrual cycle lengths in the individual,

Table 1. Reasons for exclusion from the analysis by age

	Age group (years)						
	15–19	20–24	25–29	30–34	35–39	40–44	All
No. of responders	498	456	482	473	416	536	2861
No. excluded *n*	204	313	296	225	144	153	1335
(%)	(41·0)	(68·6)	(61·4)	(47·6)	(34·6)	(28·5)	(46·7)
No. included in analysis *n*	294	143	186	248	272	383	1526
(%)	(59·0)	(31·4)	(38·6)	(52·4)	(65·4)	(71·5)	(53·3)
Reasons for exclusion*							
Hysterectomy	0	0	1	4	12	46	63
Oophorectomy	0	0	0	2	0	7	9
Combined OC	177	265	171	99	62	66	840
Progesterone-only OC	9	15	26	21	17	9	97
Pregnancy 1988	11	47	107	78	23	8	274
Birth 1988	0	25	75	42	11	2	155
Lactation 1988	0	32	93	73	27	18	243
Premenarche	9	0	1	0	0	0	10

*There were often more than one reason for exclusion in any one woman.

OC = Oral contraceptives.

although a single extreme value was ignored. For instance, if the menstrual cycles of the woman in 1988 usually varied between 26 and 31 days, and she had one single menstrual cycle of 72 days, the median of the other menstrual cycles was used as the value of her usual menstrual cycle length. In fact, this restriction was used in very few women (less than 0·5% of all). If no regular menstrual cycle pattern was found throughout the year and no usual cycle length could be defined, the woman was categorized as 'irregular' and withdrawn from the analysis of usual menstrual cycle length. The median value of maximum menstrual cycle variation in this group was 29·5 days.

Age and gynaecological age

All results regarding menstrual cycle length were analysed by age (defined as the age of the woman by 1 January 1989). As recommended by Vollman (1977), we also analysed menstrual cycle lengths by gynaecological age, defined as the age of the woman by 1 January 1989 minus the age of menarche rounded off to the nearest whole year.

Social classification

The social classification system, defined by the Danish National Institute of Social Research, was used in a simplified version with only three social groups (Hansen 1984). This classification system is based primarily on length of education, and secondly on the number of subordinates/employees and the status as employee or owner. The woman's own social group was used. School children, persons under education, and persons without any connection to the labour market were classified outside the classification system as social group O.

The study was approved by the scientific ethics committee of the County of Copenhagen.

Results

Analysis of non-responders

Non-responders tended to be older than responders, although the difference was not statistically significant ($P = 0{\cdot}093$). Significantly more responders resided in rich municipalities in the country ($P = <0{\cdot}01$). Odds ratio for high social group was 1·9 (95% CI 1·4–2·5) in responders compared with non-responders. No significant differences were found regarding cohabiting with a man, prevalence of hysterectomy, nulliparity, sterilization, former examination or treatment for infertility, or use of oral contraceptives in 1988. The prevalence of amenorrhoea did not differ significantly, odds ratio 0·6 (0·2–1·5), but the prevalence of irregular cycles in 1988 might have been lower in responders than in non-responders, although the difference was not significant (odds ratio 0·5 (0·3–1·0).

Menstrual patterns

Table 2 presents the distribution of women by age with irregular menstrual cycles or no menstrual cycles at all in 1988. Irregular cycles were seen most frequently in the youngest age group, experienced by more than 20%, but even up to the age of 30, approximately 17% had irregular cycles.

Figure 1 shows the usual menstrual cycle length in 1988 by age. Linear regression analysis showed that the cycle length decreased with increasing age ($r = 0{\cdot}23$, $P = 0{\cdot}0001$). The interindividual variation also decreased by age, the 5th to 95th centile interval decreased from 12 days in the youngest girls to 7 days in the oldest women. Linear regression showed a very close correlation between chronological and gynaecological age ($r = 0{\cdot}99$). The use of gynaecological age did not diminish the variation, which confirmed that gynaecological age grouping had no advantages over chronological age grouping.

Figure 2(a–f) shows the centile distribution of the shortest and the longest cycle length and the maximum menstrual cycle variation in regular menstruating women and in all menstruating women by age. Frequency distributions for these results and for the usual menstrual cycle length are presented in Table 3.

Usual menstrual cycle length

Very few women had a usual menstrual cycle length shorter than 21 days (0·5%) or longer than 35 days (0·9%), 12% had a cycle length between 21 and 25 days with maximum frequency in the women aged 40–44 (17·5%). Approximately 7% of all women had a usual menstrual cycle length between 32 and 35 days with a large variation by age from more than 15% in women aged 15–19 to only 2% among the oldest women.

Shortest menstrual cycle length

In women aged 20–34, the interquartile range of the shortest menstrual cycle length was rather constant (around 24–28 days), whereas the interindividual variation as such was rather high; 15·2% of regular menstruating women and 18·6% of all menstruating women experienced at least one menstrual cycle shorter than 21 days.

Longest menstrual cycle length

The median of longest menstrual cycle length decreased by age from 35 to 30 days. The interquartile range also decreased, from 31–41 days in the youngest women to 28–32 days in the oldest. The 5th–95th centile interval was large in all age groups and this was particularly marked in those under 25. In the regular menstruating women, more than 45% of the 15–19year-olds and 27·5% of those 20–24 experienced at least one menstrual cycle longer than 35 days. When all menstruating women were taken into account, the frequency rose sharply to more than 55% in the youngest women and nearly 40% in women aged 20–24.

Maximum menstrual cycle variation

The median of the maximum menstrual cycle variation in the individual decreased by age from 11 days in the teenagers to 6 days in other women, when only regular menstruating women were considered. Menstrual cycle variation as low as 0–2 days was rare, especially in the younger women. A maximum menstrual cycle variation of more than 14 days was found in one-third of regular menstruating teenagers and in approximately 10% of regular menstruating women aged ⩾ 30 years. When

Table 2. Percentage distribution of irregular cycles and no menstruation in 1988, by age.

Cycles	Age group (years) 15–19	20–24	25–29	30–34	35–39	40–44	All
Regular (%)	77·4	83·0	82·2	88·7	95·6	87·1	86·0
Irregular (%)	20·8	17·0	17·3	10·5	3·3	10·8	12·7
None (%)	1·8	0·0	0·5	0·8	1·1	2·1	1·3
No. of women	288	141	185	247	271	380	1512*

* 14 women did not answer the question.

all menstruating women were taken into account, a variation of more than 14 days was found in about 30% of all women.

Maximum menstrual cycle variation and social group

A higher frequency of maximum menstrual cycle variation of more than 14 days was found in women from the lowest social group and in women outside the social classification. In this age group, women outside the social classification were primarily the long-term unemployed and those in early retirement. The lowest frequency of large menstrual cycle variation was found in women in social group 1 (primarily persons with university education) and in social group 2 (women with more than 3 years of theoretical education and/or senior executives). Mantel-Haenzsel odds ratio regarding high menstrual cycle variation was 2·7 (95% CI 1·6–4·6) in lower class women compared with higher class women.

Assessment of the influence of social group was not possible in women aged 15–24, as few women in this age group had finished their education.

Women with and without menstrual calendar record

Table 4 shows the results from a separate analysis of the women from whom we received a complete and valid menstrual calendar record. Distribution of age and social group was identical among women with and without calendar record. The prevalence of total irregular cycles was twice as high in the group from which we received a calendar record than in the other two groups (16·7% *vs* 8·7%/8·2%). The median and the interquartile range of usual cycle length was nearly the same and the shortest menstrual cycle length showed only minor differences between the groups. Longest menstrual cycle length and maximum menstrual cycle variation were higher in the calendar group, especially when the women with irregular cycles were included in the analysis.

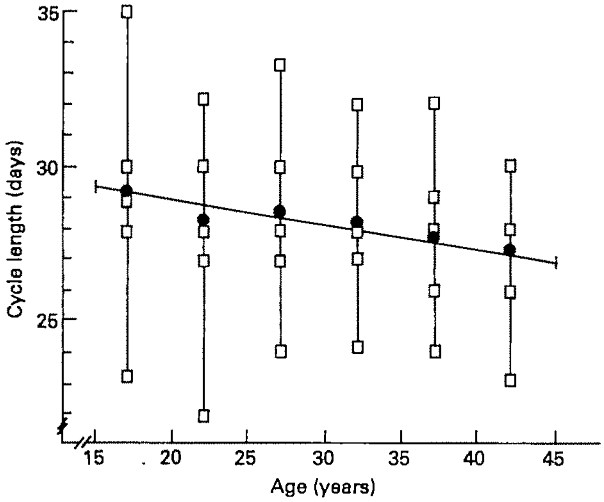

Fig. 1. Usual menstrual cycle length in 1988 by age. The mean (●) and the 5th, 25th, 50th, 75th and 95th centile values are shown (☐). Regression line ($r = 0{\cdot}23$, $P = 0{\cdot}0001$).

Discussion

A number of problems are attached to the design of studies of menstrual cycle length (Burch *et al.* 1967). Gunn *et al.* (1937), in a review of older studies, showed that retrospective studies based on hospital records have limited validity. In these studies, a mixture is found of the women's recall bias and the lack of precision in the doctor's very routine interview of the woman. In such studies, answers tend to cluster around whole weeks (e.g., 21 days, 28 days etc.). Bean *et al.* (1979) showed that even women who earlier (as participants in the study by Treolar *et al.* 1967) reported their menstrual cycle had a rather poor recall of the degree of irregularity in their menstrual patterns, especially if the events were several years past. The recall bias was greatest for the periods of life in which most irregularities were found: the postmenarcheal and premenopausal years.

In longitudinal studies there is another problem: selection bias in recruiting and in follow up. Of course, this problem is not limited to longitudinal studies, but selection bias is often of greater significance in these studies. Treolar *et al.* (1967) recruited freshmen university students and about 50% of them consented to take part in the study. The first year's calendar record, however, was only returned by about 50%. In this way, the study group might be very different from the recruitment population with regard to menstrual events.

In cross-sectional studies like those of Chiazze *et al.* (1968) and the WHO Task Force study (1983), the groups studied tended to remain intact but involved unrepresentative samples of women: the WHO study selected the women from those involved in a contraceptive study of 'natural' family planning, a method which can only be used for women whose menstrual patterns are rather regular.

In our study, a random sample of a defined age group of women from a large Danish county was drawn from the National Central Person Register. We consider that the find-

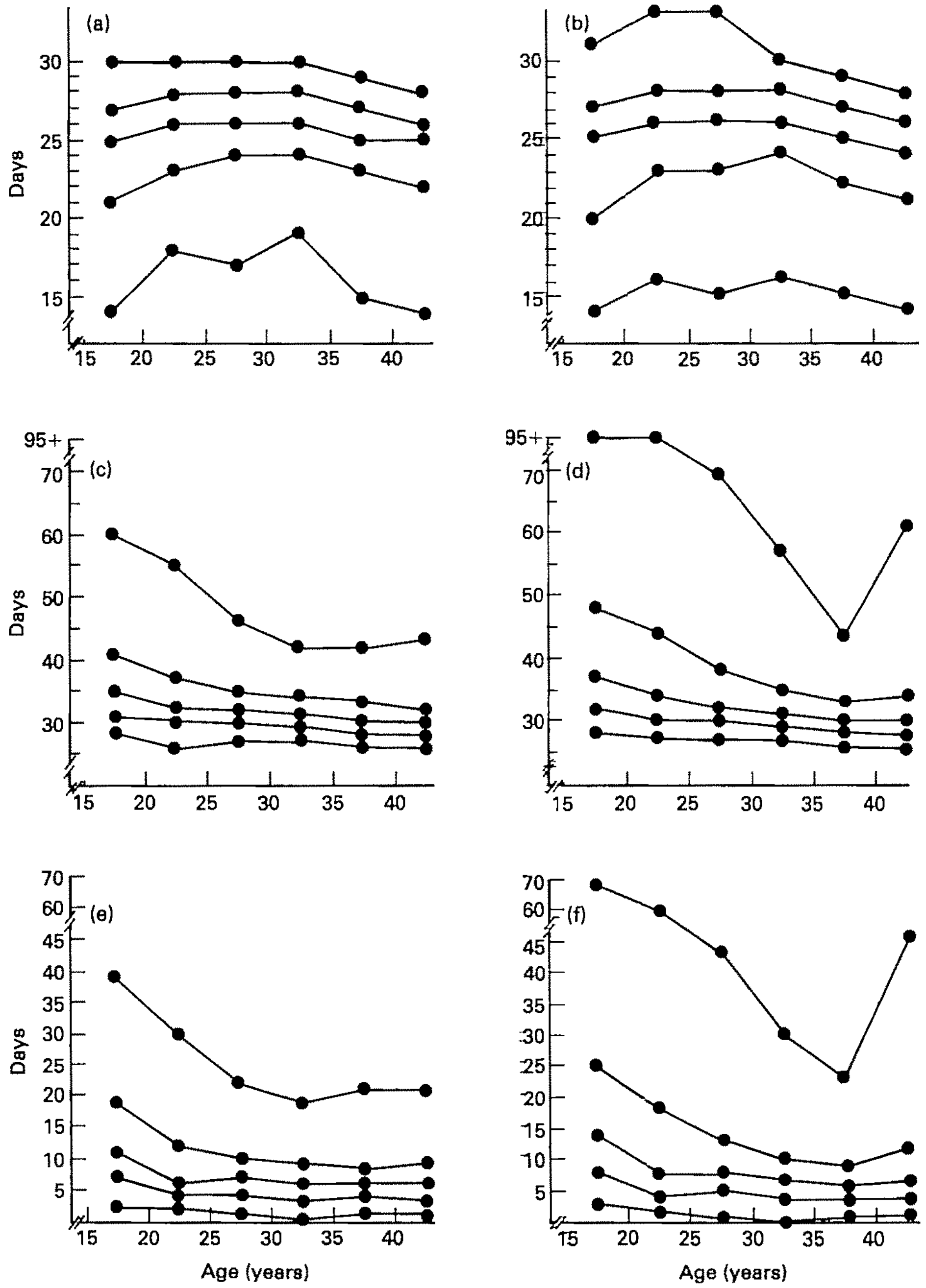

Fig. 2. Shortest, longest and maximum variation of menstrual cycle length by age in women with regular menstruations and in all menstruating women. (a) Shortest menstrual cycle length, regulars. (b) Shortest menstrual cycle length, all. (c) Longest menstrual cycle length, regulars. (d) Longest menstrual cycle length, all. (e) Maximum menstrual cycle variation, regulars (f) Maximum menstrual cycle variation, all.
The five graphs in each figure represent the 5th, 25th, 50th, 75th and 95th centile values.

ings are representative of the general population in the local area as the response rate was 78% and because telephone interviews showed that non-responders had similar characteristics. It is uncertain to what degree our results are applicable to women in other countries with different social conditions.

Our study was cross-sectional, and the data were retrospective from the immediately preceding year. A certain degree of recall bias was anticipated. In the separate analysis of data of different validity (with and without menstrual calendar record), we did in fact find some differences that supported a suspicion of misclassification due to recall bias, but the magnitude of this bias was rather small.

Our questionnaire did not include any question on 'spotting'. Unfortunately, we are therefore unable to provide data on the prevalence of this phenomena. We have no reason to believe that 'spotting' was confused with menstruation by the women, as 99·7% of the reported bleeding episodes were longer than 2 days.

In the current study, nearly half of all women had to be excluded from the analyses of menstrual patterns in 1988

Table 3. Frequency distribution of the usual, the shortest and the longest menstrual cycle lengths and maximum menstrual cycle variation by age

	Age group (years)						
Cycle length (days)	15–19 (%)	20–24 (%)	25–29 (%)	30–34 (%)	35–39 (%)	40–44 (%)	All (*n*)
Usual*							
< 21 days	0·0	0·9	0·7	0·0	0·4	1·2	7
21–25	8·5	10·3	10·5	9·6	12·3	17·5	157
26–31	74·4	78·6	79·1	83·2	80·7	79·2	1030
32–35	15·3	10·3	7·2	6·8	5·4	2·1	93
> 35	1·8	0·0	2·6	0·5	1·2	0·0	12
Shortest							
Regulars*							
< 15	6·3	3·7	2·8	1·6	3·5	4·9	44
15–20	15·2	6·6	12·4	7·9	10·5	12·7	129
21–25	29·8	33·6	33·1	38·6	41·9	48·2	445
26–31	48·2	55·1	50·3	50·3	42·8	33·5	509
32+	0·5	0·9	1·4	1·6	1·3	0·7	12
All women							
< 15	8·1	3·9	4·7	3·4	4·6	8·7	77
15–20	17·7	9·5	13·0	9·1	10·1	14·2	167
21–25	29·8	29·9	30·2	35·6	41·2	45·5	482
26–31	41·5	50·4	47·3	49·0	43·7	30·6	551
32+	2·8	6·3	4·7	2·9	0·8	0·9	36
Longest							
Regulars*							
< 26	1·6	3·9	0·0	1·6	2·2	3·3	25
26–31	25·0	39·2	45·7	57·5	63·4	66·8	592
32–35	27·7	29·4	32·9	22·9	22·5	20·1	279
36+	45·7	27·5	21·4	18·1	11·9	9·5	232
All women							
< 26	1·2	3·2	0·0	1·9	2·1	4·0	29
26–31	20·0	32·5	38·1	52·4	62·1	58·8	599
32–35	23·8	24·6	27·4	21·2	21·7	19·5	292
36+	55·5	39·7	34·5	24·5	14·0	17·7	385
Maximal cycle variation							
Regulars*							
< 3	5·9	7·8	12·9	18·1	14·1	15·9	147
3–8	26·6	56·9	51·4	54·8	61·2	54·4	576
9–14	33·5	18·6	23·6	18·1	15·4	19·1	238
15+	34·0	16·7	12·1	9·0	9·3	10·6	167
All women							
< 3	4·5	7·2	11·4	16·4	13·6	14·0	149
3–8	20·5	47·2	43·1	49·8	59·6	48·8	581
9–14	27·9	16·8	22·2	18·4	14·9	18·6	259
15+	47·1	28·8	23·4	15·5	11·9	18·9	311

*Women with regular menstrual cycles only.

because of the use of hormonal contraception, birth, pregnancy, etc. In this way, a possible selection bias might be introduced; in this age group, hysterectomy is most often undertaken due to menstrual irregularities. The frequency and probably the indication for hysterectomy as well varies from region to region in many Western countries (Anderson *et al.* 1987). In different studies, the degree to which women with irregular cycles are 'withdrawn' from the population at risk will, therefore, show similar regional variations. In this study, the frequency of hysterectomies was rather low, especially in young women.

Indeed, some women using hormonal contraception have the contraceptive prescribed to regulate their menstruation. We do not know the frequency of this indication for hormonal contraceptives in our study. A little more than a third of the women aged 15–19 were excluded because of the use of oral contraceptives, but only three girls using oral contraceptives had had no sexual intercourse. The result of withdrawing from the analysis women using hormonal contraception might render an underestimation of irregular cycles. On the other hand, the pregnant and childbearing women could constitute a rather more regular menstruating group, and the necessary withdrawal of this group of women from the analysis might tend to overestimate the irregularity in the population.

We included in the analyses women who used an intrauterine contraceptive device (IUCD). The prevalence of use of

Table 4. Comparison of certain menstrual characteristics in three groups of women with and without menstrual calendar records

	Group 1 (*n* = 620)	Group 2 (*n* = 289)	Group 3 (*n* = 617)
Age (years) mean (SD)	31·4 (9·3)	30·6 (9·4)	31·2 (9·3)
Social group (%)			
1+2	25 6	25·5	23·9
3+4	62·3	59·5	63·6
5+0	41·7	45·8	42·0
Irregular cycles (%)	16·7	8·7	8·2
Usual cycle length (days)			
Centile			
5th	25	23	23
25th	27	27	27
50th	28	28	28
75th	30	30	29
95th	33	32	32
Shortest cycle length (days) (regulars/all)			
Centile			
5th	18/16	15/14	14/14
25th	23/23	21/21	21/21
50th	25/25	25/25	25/25
75th	27/27	27/28	28/28
95th	29/31	29/29	30/30
Longest cycle length (days) (regulars/all)			
Centile			
5th	28/28	26/26	26/26
25th	30/30	28/29	28/28
50th	32/33	31/31	30/30
75th	36/40	34/35	33/35
95th	48/84	48/60	49/60
Maximum cycle variation (days) (regulars/all)			
Centile			
5th	3/3	1/1	0/0
25th	5/6	3/4	3/3
50th	8/9	6/6	5/6
75th	11/16	10/11	10/12
95th	24/51	25/32	24/32

*The groups were: 1 women who sent a complete calendar record, 2 women who stated that they had made a calendar record, but had not kept it; 3 women who had not made any calendar record.

IUCDs was 7·%, 28·3% and 22·0% in women aged 15–24, 25–34 and 35–44 respectively. IUCDs are known to increase the volume of menstrual loss, but we did not find any relation between menstrual cycle variation and use of IUCD (age-corrected odds ratio for a menstrual cycle variation of more than 14 days was 0·8 (0·5–1·1) in IUCD users).

Based on telephone interviews of a sample of non-responders, a tendency was found toward a higher frequency of irregular cycles in non-responders than in responders. This might tend to underestimate the degree of menstrual variability in the population. However, it is uncertain to which degree the observed difference was caused by the difference in questioning method (telephone *vs.* questionnaire). The non-responders, however, were more often from lower social groups than were responders, and this might result in an underestimation of the irregularity in the population as well.

In contrast to Vollman (1977), we found that chronological age was quite as good as gynaecological age in the assessment of the correlation of menstrual cycle length by age. A possible explanation might be that the results in our study arose from one single year and from a socially rather homogenous society, whereas Vollman's results were obtained from a period of more than 30 years and from persons in a heterogenous and changing society. We find the use of chronological age more clinically useful and, therefore, preferable if no special arguments exist for the utilization of a constructed measure.

In our literature review, we found no other authors who have described a correlation between menstrual cycle variation and social group. Gunn *et al.* (1937) found no difference in menstrual cycle length between different occupational groups when corrected for age. But no persons from lower social groups actually participated in their study, and they did not examine the possible correlation between menstrual cycle variation and occupation.

Table 5 compares some results from the current study to the findings of Treolar *et al.* (1967) and Vollman (1977). Comparability is complicated by the use of different units of measurement in the three studies. Treolar used the average menstrual cycle length of the individual women. Vollman used the average length of menstrual cycles, and we used the usual menstrual cycle length of the individual women, which in most cases was identical to the median value. Because of the choice of usual menstrual cycle length as a unit, we had to exclude from the analysis the women in whom a description of a usual menstrual cycle length was meaningless. Especially in the youngest age group, our method resulted in a somewhat lower mean value, as women with irregular menstrual cycles had a higher frequency of very long menstrual cycles. In Vollman's study, each of these long menstrual cycles counted separately, resulting in the finding of the longest cycle length in his study. The inter-individual variation of menstrual cycle length is lowest in our study, although still considerable.

We find that the biggest advantage of our method is that it resembles the clinical interview situation as it is rarely possible to obtain information from patients of an average menstrual cycle length for a given period of time.

Our study confirms the normally used definitions of polymenorrhoea (cycle length <21 days) and oligomenorrhoea (cycle length between 36 and 90 days), as these very short or

Table 5. Comparison of the results in current study with those of two older studies*

	Cycle length (days)		
	Current	Treolar	Vollman
Age 15–24			
Mean (SD)	28·8 (2·9)	30·4 (4·1)	30 1
5th–95th centile range	23–34	25–39	21–44
Age 25–34			
Mean (SD)	28·4 (2·6)	29·3 (3·1)	29·7
5th–95th centile range	24–33	24–36	23–39
Age 35–44			
Mean (SD)	27·5 (2·4)	27·7 (2·8)	28·1
5th–95th centile range	23–31	24–33	22–36

Treolar *et al.* (1967) and Vollman (1977) The calculation in age groups was made by us from the raw figures in the two studies (Treolar, p. 99, Vollman pp. 56, 101).

very long cycle lengths were indeed very seldom recorded for a longer period in this large population of normal women. We could not, however, confirm the widely held view of low intra-individual menstrual cycle variation in normal women. Weingold (1990) considered a menstrual cycle variation of ≥ 5 days to be a sign of disturbance in the feedback and control mechanism of the hypothalamic-pituitary-ovarian axis. Many gynaecologists even consider it suggestive of disease. If this were true, about two-thirds of normal Danish women aged 15 to 44 would be suspected of disease or at least of some kind of feedback/control disturbance. Obviously, we are not able to prove that these women are not sick, but the proportion alone renders this possibility highly improbable.

In a study of all women admitted to hospital in Tasmania in 1987 and 1988 for investigation of abnormal uterine bleeding and in which a dilatation and curretage was performed, Allen *et al.* (1990) found a total of four women with endometrial cancer among the 4280 premenopausal women, and they all were in the group with post-coital bleeding, a symptom which in itself would lead to a suspicion of organic disease, even in the absence of other menstrual disturbances. Considering the high prevalence of high intra-individual variation in menstrual cycle length and the high frequency of total irregular cycles, it may be time to reconsider the need for surgical intervention in younger women with menstrual irregularities (except for post-coital bleedings) when the gynecological examination and a cervical smear are both normal.

Acknowledgments

The study has received financial support from: The Augustinus Fund; The August Pedersen Fund; The Danish Council for Research Policy and Planning, Grants for Women Research; The Danish Health Fund; The Danish Hospital Foundation for Medical Research, Region of Copenhagen, The Faroe Islands and Greenland; The Danish Insurance Association; The Danish Medical Research Council; The Fund of Else and Mogens Wedell-Wedellsborg; The Fund of Jacob Madsen and wife, Olga Madsen; The Fund for Special Affairs of the Credit Association 'Denmark'.

Dr Münster was supported by a research fellowship at the University of Copenhagen.

We would like to thank all the women who participated in the study.

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Received 18 March 1991
Accepted 29 October 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 430–433

REPRODUCTIVE SCIENCE

Secondary amenorrhoea: prevalence and medical contact—a cross-sectional study from a Danish county

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ABSTRACT

Objective To examine the prevalence of secondary amenorrhoea and the patterns of seeking medical advice for secondary amenorrhoea in an unselected population.
Design Cross-sectional postal questionnaire study.
Setting County of Copenhagen, Denmark.
Subjects 3743 women, aged 15–44, selected at random from a Danish county who were asked to provide information on menstrual patterns for the preceding year, 1988. The response rate was 78%. Information from non-responders was obtained via telephone interviews.
Results One-year period prevalence of secondary amenorrhoea of more than 3 months duration was 4·6% and was 7·6%, 3·0%, and 3·7% in women aged 15–24, 25–34, and 35–44 respectively. The duration of secondary amenorrhoea was 6 months or less in 75% aged 15–34 years, but longer than 6 months in 55% of those aged 35–44 years. A social gradient was found of the prevalence of secondary amenorrhoea (odds ratio 3·3, 95% CI 1·5–8·3) in the lowest social group compared with the highest social group; controlled by age. Only 39% of women with secondary amenorrhoea had contacted a doctor. Educational level or social status did not seem to influence the frequency of medical contact in women with amenorrhoea.
Conclusion Spontaneous return of the menstrual cycle occurs within 6 months in many amenorrheic women below the age of 35. The detailed investigation of secondary amenorrhoea in this age group can be postponed until it is of 6 months duration, unless there is clinical suspicion of disease. The relative infrequency with which women with secondary amenorrhoea seek medical advice constitutes an important source of selection bias in hospital-based clinical research on this topic.

Knowlege of the prevalence of secondary amenorrhoea and other menstrual disturbances in the general population is sparse. We are aware of only one representative population survey on this topic, a study by Pettersson *et al.* (1973) on the prevalence of secondary amenorrhoea in a Swedish county. The aetiology and prognosis of secondary amenorrhoea have been investigated primarily in women attending gynaecological specialist care (Franks 1987; Hirvonen 1977). It is unknown how many of the women with amenorrhoea seek medical advice at all. Among women visiting their general practitioner because of secondary amenorrhoea probably only a few are referred to a gynaecologist. The selection bias in specialist-care based studies might therefore be rather high. As part of an investigation on the epidemiology of menstrual patterns among women of fertile age in a large Danish county, we examined the prevalence in one year, 1988, of amenorrhoea and of medical consultation by women with amenorrhoea.

Subjects and methods

The study population comprised 3743 women, aged 15 to 44, resident in Copenhagen county, selected at random from the National Central Person Register. The women received a postal questionnaire in spring 1989. The response rate was 78%.

A short, structured telephone interview was conducted in a sample of non-responders. Non-responders were in general from lower social groups than responders. A slightly higher (although not statistically significant) prevalence of amenorrhoea and of irregular cycles were found in non-responders compared with responders.

In the analyses of menstrual data, the following persons were excluded: premenarcheal women, women using oral contraceptives in 1988, women who had been pregnant, had given birth, or had been lactating in 1988, and hysterectomized and bilateral oophorectomized women. Subsequently, 1526 women remained for the analyses.

We have given a more complete account of the structure of the study and the analyses of non-responders (Münster *et al.* 1992).

Statistical methods

Data were processed using the standard computer programs SPSS (Norusis 1988) and Medstat (Wulff & Schlichting 1988). Ferquency distributions were used in aged-divided analyses. Mantel-Haenszel's test was used for testing age-dependent variables. In the other analyses, the χ^2 test, with Yates'

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correction when appropriate, or Fisher's exact test for 2 × 2 tables, were used.

Definitions

Amenorrhoea. This was defined as the cessation of menstrual bleedings for more than three successive months in the calendar year 1988. As the premenarcheal women were excluded from the analyses, only secondary amenorrhoea was analysed. *Irregular cycles.* These were defined in one of two ways. In women from whom we received a complete and valid calendar record, the values of the calendar record were used, and the menstrual cycle of the woman was defined as irregular if no regular menstrual interval pattern was found throughout the year and no usual cycle length could be defined. The median menstrual cycle variation in the group was 29·5 days. In women from whom we obtained no calendar record, irregular cycles were defined as the woman's answer in the questionnaire 'My menstrual cycles are totally irregular, without any fixed time patterns.'

Social classification

The social classification system, defined by the Danish National Institute of Social Research, was used in a simplified version with only three social groups (Hansen 1984). This classification system is based primarily on length of education and secondly on the number of subordinates/employees and status as employee or owner. The woman's own social group was used. School children, those still being educated, and unemployed women were classified outside the classification system as social group 0.

The study was approved by the scientific ethics committee of the County of Copenhagen.

Results

Table 1 presents the prevalence and duration of secondary amenorrhoea 1988, by age. Secondary amenorrhoea was found in 70 (4·6%) of 1521 women. The prevalence differed significantly between the three age groups ($P = 0{\cdot}0017$). The range of duration was 3 months to 8 years. Secondary amenorrhoea of more than 6 months duration was found in 1·6% of the women (1·8%, 0·7% and 2·0% in women aged 15–24, 25–34 and 35–44 respectively). The duration was significantly shorter in women under 35 years ($P = 0{\cdot}041$).

Table 2 shows the relation, controlled for age, between the duration of secondary amenorrhoea and the seeking of medical advice. Around 40% of the women with secondary amenorrhoea had contacted a doctor (30·3% in the 15–24 years old, 38·5% in the 25–34 years old, and 50·0% in the 35–44 years old). No association was found between longer duration and the tendency to consult a doctor (odds ratio 0·4 (0·1–1·2)). Educational level and social status did not influence the seeking of medical advice ($P = 0{\cdot}41$).

Table 3 shows the prevalence, controlled for age, of secondary amenorrhoea and of irregular cycles in cohabiting and non-cohabiting women. Age-specific odds ratio exhibited a parallel tendency, that the prevalence of amenorrhoea and of irregular cycles was lower in cohabiting women in the younger age groups, whereas the prevalence was higher in cohabiting women over the age of 35. However, the confidence limits overlapped, and the age-corrected odds ratio showed no association (odds ratio for secondary amenorrhoea 1·0 (95% CI 0·5–2·1); odds ratio for irregular cycles 1·3 (95% CI 0·9–2·1)).

Fig. 1 presents the prevalence of secondary amenorrhoea and irregular cycles in women aged 25–44 by social group. A higher frequency of both amenorrhoea (odds ratio 3·3 (1·5–8·3)) and irregular cycles (odds ratio 4·7 (2·5–9·0)) was found in the lowest social groups compared with the highest social groups. In this analysis, women from the lowest social group (5) were combined with those who were outside the social group classification, as the latter in this age group primarily comprise the long-term unemployed and those in early retirement. The frequency of menstrual disturbances among women from the two groups was largely identical. Assessment of the influence of social group was not possible in women under 25 years, as few women in this age group had finished their education.

We asked the women with secondary amenorrhoea whether they considered themselves to be menopausal and whether they experienced any of a series of probable oestrogen-deficiency related symptoms. Only one woman under 35 considered herself menopausal, whereas 80% of women over 35 considered themselves menopausal. An association was found between the duration of amenorrhoea and the suspicion of menopause in the women ($P = 0{\cdot}049$), but the association was most probably due to the different age distribution in women with shorter and longer duration. In women aged 35–44 the association between the women's view of their menopausal status and oestrogen-deficiency symptoms was assessed. Symptoms were reported by a varying percentage of the women (hot flushes by 78%; night sweating by 53%; irritability by 59%; difficulties concentrating

Table 1. Prevalence and duration of secondary amenorrhoea, by age

	Age group (years)		
Amenorrhoea	15–24 (*n* = 434)	25–34 (*n* = 432)	35–44 (*n* = 655)
Prevalence	7·6%	3·0%	3·7%
Duration (months)			
3–6	5·8%	2·3%	1·7%
7–12	1·4%	0·2%	1·1%
>12	0·4%	0·5%	0·9%

Prevalence by age: χ^2 12·72, df 2, $P = 0{\cdot}001$.

Table 2. Association between the tendency to consult a doctor and duration of amenorrhoea, by age

Age group (years)	Duration of amenorrhoea (months)	No. of women	Medical consultation	
			Yes	No
15–24	3–6	25	36·0	64·0
	>6	8	12·5	87·5
25–34	3–6	10	30·0	70·0
	>6	3	66·7	33·3
35–44	3–6	11	72·7	27·3
	>6	13	30·8	69·2

Odds ratio (Mantel-Haenszel) for medical contact in women with secondary amenorrhoea >6 months 0·4 (95% CI 0·1–1·2)

Table 3. Frequency of amenorrhoea and irregular cycles in women living with or without a male partner, controlled by age*

		Living with a man		
Variable	*n*	Yes	No	Odds ratio (95% CI)
Amenorrhoea (%)				
Age group (years)				
15–24	434	5·4	8·1	1·5 (0·6–4·0)
25–34	432	2·9	3·3	1·1 (0·3–3 6)
35–44	655	4 0	1·9	0·5 (0·1–1·9)
Corrected for age				1·0 (0·5–2·1)
Irregular cycles (%)				
Age group (years)				
15–24	434	12·3	21·4	1 9 (0·9–3·9)
25–34	432	12 4	15·4	1 3 (0·7–2·6)
35–44	655	8 0	6·9	0·9 (0·5–1·5)
Corrected for age				1·3 (0 9–2·1)

*We asked whether or not the woman was living with a husband or male partner.

by 47%; and vaginal soreness by 18%). We found no association between the women's reporting of menopause-suspected symptoms and their own view of whether they considered themselves to be menopausal (*P* for Fisher's exact test varied between 0·67 and 1·0).

Discussion

Some researchers (such as Bean *et al.* 1979) have seriously questioned the ablity of women to recall their previous menstrual patterns, especially over long intervals of time. However, distinct events like amenorrhoea might be remembered more easily than repetitive patterns (WHO 1981). In the current study, the collection of data was retrospective, but the women were reporting the events of the immediately preceding year with only a few months delay. More than 60% of the women with secondary amenorrhoea, moreover, sent us their menstrual calendar for the year. Recall bias was considered negligible.

Telephone interviews with a sample of non-responders showed a slightly higher prevalence of secondary amenorrhoea in non-responders than in responders, although the difference was statistically not significant. The effect of this potential selection bias is likely to have been trivial. If we assume all non-responders to have the same prevalence of secondary amenorrhoea as interviewed non-responders, then the 'true' prevalence in the population would increase from 4·6% to 5·4%.

In the current study, the one-year period prevalence of secondary amenorrhoea was 4·6%. This corresponds well to the findings of a one-year period prevalence of 4·4% reported by Pettersson *et al.* (1973). Both of the studies were representative population surveys, but it is not possible to draw a direct parallel between the findings. Pettersson *et al.* (1973) included in their population at risk women who had been pregnant and women using oral contraceptives in the study year, with six months each. It is not clear, whether women with no withdrawal bleeding during the use of oral contraceptives and women with physiological amenorrhoea post-partum and during lactation were included as secondary amenorrhoea. To avoid this problem, we chose to exclude from our analyses women with a surgical menopause, those using oral contraceptives and women who had been pregnant, had given birth, or had been lactating during the year. Of the 974 women who used oral contraceptives for some period during 1988, 30 (3·1%) reported lack of withdrawal bleeding for more than 3 months in 1988, but only 8 (0·8%) users of oral contraceptives had secondary amenorrhoea immediately following the use of oral contraceptives.

We are not aware of any other study examining the frequency of medical consultation in women with secondary amenorrhoea. We found that only about 40% of the women with secondary amenorrhoea had contacted a doctor. A modest, but non-significant tendency was found towards a higher consultation-rate in older women. The consultation-rate was not influenced by the duration of amenorrhoea, and was not associated with educational level or social group. These results might reflect a type 2 error, but we find it more probable that the decision of a woman to seek medical advice for secondary amenorrhoea is influenced primarily by her interpretation of the meaning of the symptom. Further research on this topic would necessitate the application of qualitative interview techniques.

Fries *et al.* (1974) found a higher frequency of university education in a group of amenorrhoic women compared with an age-matched control group (37% *vs* 15%), and housewives were half as frequent (15% *vs* 34%). In contrast, we found the lowest prevalence of secondary amenorrhoea and irregular cycles in women from the highest social groups. We were not able to assess the menstrual cycle variations in housewives, as only 1% of all women in our study group were housewives. The low prevalence of housewives in our study group is not surprising as more than 90% of younger women in Denmark are engaged in either education or occupational work with even higher prevalence in urban areas, such as that on which our study was based. We have no clear explanation for the difference between our results and those of Fries *et al.* (1974), but if we assume that variation in the length of cycle is associated with stressful life circumstances (reviewed by Drew 1961), the difference in social groups found in our study is consistent with studies of the social distribution of other stress-related symptoms in the population (Rasmussen *et al.* 1988).

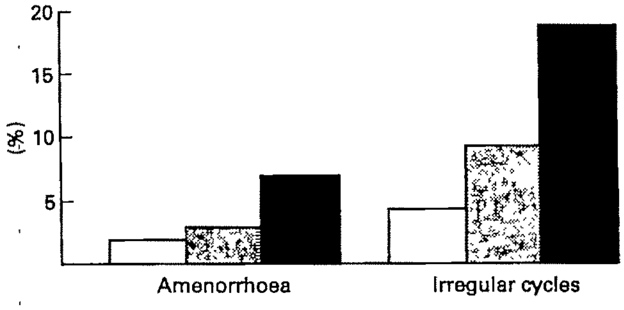

Fig. 1. Frequency of amenorrhoea and irregular cycles 1988 in women aged 25–44, by social group. □, social group 1 + 2; □, social group 3 + 4, ■, social group 5 + 0. Odds ratio (Mantel-Haenszel) for the frequency of amenorrhoea 3·3 (1·5–8 3) and irregular cycles 4·7 (2·5–9·0) in social group 5 + 0 *vs* social group 1 + 2.

Some researchers (such as Cutler *et al* 1980) have reported an association between stable ongoing sexual behaviour patterns and regularity of the menstrual cycle. Two possible explanations for this association were suggested: a feedback LH response to coital activity with or without a female endocrine response to male pheromones. We failed to demonstrate significant association between the prevalence of secondary amenorrhoea or irregular cycles and cohabitation patterns of women. However, the youngest women living without a male partner tended to have a higher prevalence of menstrual irregularity. The most reasonable hypothesis for this result is a selection effect. Early menarche was shown by Helm & Lidegaard (1989) to correlate with increased sexual activity. Thus, in younger women gynaecological maturity might influence the frequency of permanent cohabiting and thereby increase sexual activity. Stable menstrual patterns might be the cause for the association between menstrual regularity and sexual behaviour rather than the effect.

We found that in 75% of the women <35 years of age the duration of amenorrhoea was shorter than 7 months, and only one third of these women contacted a doctor. This result may assist the choice of diagnostic and therapeutic strategy for this age group. There is a clear tendency for a spontaneous cure of amenorrhoea of shorter duration. In a consecutive study of normal pregnant women Westman (1958) found that 106 of 2262 (4·7%) had earlier experienced amenorrhoea. Among these 106 women, 55 had experienced secondary amenorrhoea of less than 6 months duration after the first postmenarcheal year, and only two of them had had any treatment for their condition. The rest of the women had spontaneously recovered ovulatory function, as demonstrated by their ability to become pregnant. Westman's data cannot be used to estimate the prevalence of secondary amenorrhoea, as his study group comprises only the 'winners', leaving the 'failures' out, but the study demonstrates that a rather high proportion of normal pregnant women in some period in their lives have had secondary amenorrhoea and that ovulatory function recovered more often spontaneously than as a result of medical treatment. It might be asssumed that most episodes of brief amenorrhoea are caused by functional endocrinological (control/feedback) disturbances, related to a broad spectrum of life circumstances in the women (such as weight change, sports activities and psycho-social stress) and require no therapy.

In contrast, therapy might be indicated for longer lasting secondary amenorrhoea because the accompanying hypooestrogenaemia might increase the risk of osteoporosis; no negative effects of shorter lasting amenorrhoea have been demonstrated (Drinkwater *et al.* 1986; Jones *et al.* 1985). An expectant strategy with a 3-month follow up appointment would be fully warrantable in these patients, unless the medical story, and the physical and gynaecological examination suggest the possibility of organic disease. in this way, detailed and costly investigations might be omitted in about 75% of women under 35 years with secondary amenorrhoea.

Acknowledgments

The study has received financial support from: the Augustinus Fund; The August Pedersen Fund; the Danish Council for Research Policy and Planning, Grants for Women Research; The Danish Health Fund; The Danish Hospital Foundation for Medical Research, Region of Copenhagen, The Faroe Islands and Greenland; The Danish Insurance Association; The Danish Medical Research Council; The Fund of Else and Mogens Wedell-Wedellsborg; The Fund of Jacob Madsen and wife, Olga Madsen; The Fund for Special Affairs of the Credit Association 'Denmark'.

Dr Münster was supported by a research fellowship at the University of Copenhagen. We would like to thank all the women who participated in the study.

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Received 18 March 1991
Accepted 20 October 1991

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 434–438

FERTILITY CONTROL

A double-blind randomized study of the effect of erythromycin in preventing pelvic inflammatory disease after first trimester abortion

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ABSTRACT

Objective To assess the prophylactic use of erythromycin in prevention of post-abortal pelvic inflammation disease (PID) in first trimester abortion.
Design Double-blind, randomized controlled trial.
Setting Department of Surgery, County Hospital, Denmark.
Subjects Four hundred and thirty two women who were to undergo induced abortion before 12 weeks gestation were randomized to be treated either with prophylactic erythromycin or a placebo.
Intervention The women were randomized to receive a placebo or erythromycin, 500 mg twice a day for 7½ days starting the evening before the abortion. All the women were investigated for *Chlamydia trachomatis* and *Neisseria gonorrhoea* before the abortion.
Main outcome measures Frequency of cervical *C trachomatis* and *N gonorrhoea* and frequency of PID after abortion.
Results Fifty four women were excluded after randomization. The frequency of PID was 11% (20/189) in the erythromycin group and 16% (30/189) in the placebo group ($P = 0{\cdot}13$, χ^2-test). The prevalence of *C. trachomatis* was 19% (15/78) in women ≤20 years of age, 13% (14/109) in women between 21 and 25 years and 2% (5/241) in women ≥26 years of age. In women positive for *C. trachomatis* erythromycin prophylaxis significantly reduced the frequency of PID to 8% (1/13) compared with 43% (6/14) in the placebo group ($P = 0{\cdot}051$, logistic regression analysis). Erythromycin had no effect on other potential high risk groups (first pregnancy, nulliparous, <20 years of age. and women with previous PID).
Conclusion Prophylactic erythromycin is not warranted for all women having an abortion. Cervical *C. trachomatis* is a risk factor for postabortal PID, and prophylaxis with erythromycin significantly reduces the frequency of PID. However, only a few women with PID had cervical *C. trachomatis*, and the prevention of post-abortal PID remains a major challenge requiring further studies.

Pelvic inflammatory disease (PID) is the most frequent complication after induced abortion. It can be caused by several different pathogens. Among these are the exogenous sexually transmitted agents, such as *Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma hominis* and *Ureaplasma urealyticum,* and the endogenous perianal vulvovaginal flora (Mårdh 1980; Burnakis *et al.* 1986; Weström 1987). *C trachomatis* is accepted as the most common pathogen in PID (Weström & Mårdh 1983; Westrom 1987) and its presence in the cervical canal at the time of an abortion is an important risk factor for postabortal PID (Qvigstad *et al.* 1982, 1983; Westergaard *et al* 1982; Osser & Persson 1984; Møller *et al.* 1982; Heisterberg 1987; Levallois & Rioux 1988; Osser & Persson 1989).

The use of prophylactic antibiotics in preventing postabortal PID is disputed (Ledger 1983; Grimes *et al.* 1984).

In Denmark, women seeking induced abortion are not routinely screened for *C. trachomatis* (Prien-Larsen & Kjer 1989).

The purpose of the present study was to assess the prophylactic use of erythromycin (Abboticin) in the prevention of postabortal PID among all women undergoing first trimester induced abortion, with special attention to those at high risk of postabortal PID. Erythromycin was chosen because it is active against most of the vaginal flora and particularly effective against *C trachomatis.* Erythromycin, together with the relevant treatment for gonocci, is standard treatment for PID in Denmark.

Subjects and methods

This was a double-blind randomized prospective study and

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432 women who were to undergo induced abortion participated with informed consent. They were given either placebo or erythromycin 500 mg twice a day for 7½ days (15 doses), starting the evening before the abortion. Randomization was arranged by Abbott in consecutively numbered blocks of tablet boxes. The study ran from October 1985 to March 1988.

Women who were allergic to erythromycin, who had had antibiotic treatment during the week before the abortion and who showed signs of infection were excluded before randomization.

The trial was approved by the regional ethics committee and the National Board of Health.

Patient assessment and collection of specimens

The women were assessed and allocated to their treatment a few days before the abortion. Gestational age (weeks of amenorrhea), current contraceptive method, parity, previous miscarriages and induced abortions and any previous sexually transmitted disease (STD) or PID were recorded.

An unlubricated speculum was used to sample the cervix for *C trachomatis* with a dacron-tipped swab; specimens for *N. gonorrhoea* were taken from the cervix and urethra with charcoal-tipped swabs.

All clinical and laboratory personnel were blind to the treatment allocation. The results of the *C trachomatis* tests were blinded.

Microbiological studies

C. trachomatis was detected by immunological methods. In the first half of the study, direct immunofluorescence microscopy (Syva Micro-Trac) was used, but this was later replaced by enzyme immunoassay (Chlamydiazyme Abbott). Culture specimens for *N. gonorrhoea* were transported in Stuart's media and were inoculated on a selective chocolate agar and confirmed by direct immunofluorescence. Women with a positive gonococcal culture were treated and excluded from the study.

Operation

The abortions were performed before 12 completed weeks gestation. The vagina was cleaned with 0·1% cetrimide solution. After cervical dilatation and vacuum aspiration, a blunt curettage was used and methylergometrine 0·2 mg was given intravenously.

Patient follow-up

Before discharge each woman received a follow-up sheet and was instructed to contact her general practitioner 1 week after the abortion and after the first menstruation, or at any time if she suspected complications. Compliance was checked by asking general practitioners to count any remaining tablets. The general practitioner did not know the results of the *Chlamydia* test or to which treatment the women had been allocated. Those women who did not attend follow-up visits were contacted by telephone or mail.

Definition of PID

The general practitioners were instructed to make a diagnosis of PID if the women developed lower abdominal pain plus at least two of the following characteristics: tenderness of uterus, tenderness of tubes, adnexal masses, abnormal discharge, abnormal bleeding, and fever above 38°C.

Statistical methods

χ^2-tests and Fisher's exact test (two-sided) were performed. The effect of erythromycin prophylaxis was analysed in five different potentially high risk groups: *C. trachomatis*-positive women, first pregnancies, nulliparous, women aged <20 years and women with previous episodes of PID. The analysis took into account the unequal representation of risk groups in the placebo and erythromycin group. This was done by logistic regression analysis, which was performed by stepwise backward elimination starting with a model where only two factor interactions (treatment by risk factor) were included (BMDP Statistical Software Manual 1983; Agresti 1984). Analysis of odds ratios were performed by exact test to assess whether the treatment effect was different in the high risk group compared to the non-high risk group (StatXact manual 1989; Agresti 1984).

The therapeutic gains were calculated with 95% confidence intervals (CI) and estimated by an approximation to the normal distribution.

The number of women recruited for the trial was based on an expected prevalence of postabortal PID of 17% in the placebo group (based on a pilot study), and an estimated reduction of 10% to a prevalence of 7% in the treatment group. By including 163 women in each group, this difference would be demonstrated with a type 1 error of 0·05 and a type 2 error of 0·2.

Results

Study population

Of the 432 women randomized, 54 (12%) were excluded after randomization (Table 1). The decision about exclusion was taken without knowing to which group the woman was allocated. A total of 31 women failed to take the medication, 11 in the erythromycin group and two in the placebo group stopped medication because of adverse effect, and five women in the erythromycin group and 13 in the placebo group forgot to take their medicine. These 31 women are included in the analysis in their allocated groups. The final analysis was based on 378 women. The 54 women excluded from the analysis were significantly younger than the others: 31% (17/54) were ≤20 years old compared with 16% (62/378) ($P = 0{\cdot}007$) (median age 23 years and 28 years, respectively). Those excluded did not differ in relation to frequency *C. trachomatis* in cervix, parity, previous PID, previous STD, or gestational age (data not shown).

Follow-up

Of the 378 women included in the study, 241 (64%) came to both follow-up visits, 91 (24%) attended only one follow-up visit and were later contacted by telephone or mail and 46 (12%) were reached by telephone or mail only.

Comparability of the two randomized groups

The placebo and erythromycin group were comparable (Table 2).

Table 1. Reasons for exclusion after randomization

	All (n = 54)	Erythromycin (n = 27)	Placebo (n = 27)
Regretted giving consent*	7	5	2
Concurrent sterilization, miscarriage, ectopic pregnancy etc.*	15	7	8
Received another antibiotic*	10	5	5
Drop outs, could not be traced	10	5	5
Data not available	12	5	7

*Exclusions done according to the protocol.

Prevalence of C. trachomatis and N. gonorrhoea

C trachomatis was isolated from the cervix in 34 (8%) of the original group of 428 women seeking induced abortion. The prevalence was significantly higher in younger women, as 19% (15/78) of those ≤20 years of age, and 13% (14/109) of those between 21 and 25 years of age carried *C. trachomatis*, compared with only 2% (5/241) of the women ≥26 years of age (P<0·0005), χ^2-test). *N gonnorrhoea* was isolated from 1% (3/431). Two women were infected with both organisms.

Effectiveness of prophylaxis

The frequency of postabortal PID was 10·5% in the erythromycin group and 15·9% in the placebo group (P = 0·129, χ^2-test). The therapeutic gain was 5·3% (95% CI 1·6%–12·1%).

Logistic regression analysis showed that women who had had a previous episode of PID (P = 0·053) or were ≤20 years of age (P = 0·047) were significantly more at risk of postabortal PID. However, the subgroup analysis by logistic regression did not confirm that erythromycin had a specific effect in prevention of postabortal PID in these two potentially high-risk groups.

Although the univariate analysis (Fisher's exact test) indicated that erythromycin reduced the frequency of postabortal PID significantly in those with first pregnancies (P = 0·037) (Table 3), these findings were not confirmed by the other statistical tests, since the effect was dependent on the treatment effect in the *C. trachomatis* positive women (Table 3).

Table 2. Characteristics of the women in the two study groups

	Erythromycin (n = 189)		Placebo (n = 189)		P*
Age (years) median range	28	(14–46)	27	(14–46)	
75%–25% quartiles		22–34		21–36	
	n	(%)	n	(%)	
Nulliparae	73	(39)	87	(46)	0·18
First pregnancy	61	(32)	68	(36)	0·51
Gestation ≥11 weeks	34	(18)	21	(11)	0·06
Previous PID	50	(26)	40	(21)	0·28
Previous STD	18	(10)	9	(5)	0·11
Positive *Chlamydia*-test	13	(7)	14	(7)	0·83

*χ^2-test.
PID, pelvic inflammatory disease.
STD, sexual transmitted disease.

In *C. trachomatis*-positive women we found a borderline significant effect of erythromycin in preventing postabortal PID, as 43% of those in the placebo group developed PID compared with 8% in the erythromycin group (P = 0·079, Fisher's exact test) (Table 3). The therapeutic gain from erythromycin treatment in *C. trachomatis* positive women was 35·2% (95% CI 2·4%–68·0%). Logistic regression analysis confirmed that the effect of erythromycin differed significantly between *C. trachomatis*-positive and negative women (P = 0·051) (Table 3).

Discussion

Treatment with erythromycin 500 mg twice daily starting the evening before the abortion reduced the frequency of postabortal PID to 11% compared with 16% in the placebo group, this difference was not significant. Although the lack of significance may be explained by the small size of the study population, a therapeutic gain of 5·3% does not warrant antibiotic treatment of all women undergoing induced abortion. A few randomized controlled studies have shown significant reductions in the frequency of postabortal PID associated with prophylactic antibiotic treatment (Sonne-Holm *et al.* 1981; Levallois & Rioux 1988; Darj *et al* 1987). However, common to these studies were modest therapeutic gains (2·6%–4·1%), indicating that many women received unwarranted antibiotic treatment.

On the other hand, the high frequency of postabortal PID, with potential long-term risks of chronic pelvic pain, dyspareunia (Heisterberg *et al.* 1986), subfertility and ectopic pregnancy (Hogue 1986) indicates the need for identification of women at high risk of postabortal PID and assessment of the effect of prophylactic antibiotics.

Several studies have suggested, but not unequivocally proven, that the following are risk factors for postabortal infection: age <20 years (Tietzte 1972; Cheng *et al* 1977), previous PID (Sonne-Holm *et al.* 1981; Darj *et al.* 1987), no previous pregnancy (Cheng 1977; Heisterberg & Kringelbach 1987), nulliparity (Cheng 1977; Nesheim 1984; Park 1985; Heisterberg & Kringelbach 1987) and nulliparity associated with two or more sex partners (Levallois & Rioux 1988). In our study women with previous episodes of PID and ≤20 years of age had a significantly higher risk of postabortal PID, but erythromycin prophylaxis did not have any effect on these women, nor did it have an effect on nulliparous women or in those with no previous pregnancies. However, the women who dropped out of the study after randomization were predominantly those aged ≤20 years. Future studies should take special care to minimize the risk of younger women from dropping out.

The only subgroup in which erythromycin prophylaxis was significantly effective was the *C. trachomatis*-positive subgroup. Our data showed that cervical *C. trachomatis* was a risk factor for postabortal PID, as 43% of the infected women in the placebo group developed PID, compared with only 8% in the erythromycin group. In other studies postabortal PID was reported in 15%–28% of women harbouring *C trachomatis* (Qvigstad *et al* 1982, 1983; Møller *et al.* 1982; Westergaard *et al.* 1982; Osser & Persson 1984; Levallois & Rioux 1988).

The high prevalence of asymptomatic cervical *C. trachomatis* in the younger women seeking abortion was similar to other

Table 3. Infection rate and effectiveness of prophylaxis in women at risk of postabortal pelvic inflammatory disease (PID)

Factors		Erythromycin (n = 189)		Placebo (n = 189)		Odds			
	n	n	(%)	n	(%)	ratio	P*	P†	P‡
Chlamydia-positive									
Yes	27	1/13	(8)	6/14	(43)	9·000	0·077	0·218	0·051
No	348	19/175	(11)	23/173	(13)	1·259	0·514		
Previous episodes of PID									
Yes	90	7/50	(14)	8/40	(20)	1·536	0·571	0·129	0·447
No	288	13/139	(9)	22/149	(15)	1·679	0·206		
Age (years)									
≤20	62	2/24	(8)	12/38	(32)	5·077	0.059	0·220	0·274
>20	316	18/165	(11)	18/151	(12)	1·105	0·860		
Parous									
No	160	8/73	(11)	18/87	(21)	2·120	0·132	0·172	0 285
Yes	218	12/116	(10)	12/102	(12)	1·156	0·829		
Previous pregnancy									
No	129	6/61	(10)	17/68	(25)	3·056	0·037	0·171	0·257
Yes	249	14/128	(11)	13/121	(11)	0·980	1·000		

*Treatment effect by univariate test (Fisher's exact test, two-sided).

†Treatment effect by test for homogeneity of odds ratio (OR) and estimation and subsequent testing of common OR equal to one (exact test).

‡Treatment by risk factor interaction. Logistic regression analysis. See text.

Backward elimination resulted in: erythromycin treatment by *C trachomatis* positive (P = 0·051) and the main effects of previous episodes of PID (P = 0·053) and of age (P = 0·047).

studies (Westergaard *et al.* 1982; Qvigstad *et al.* 1983; Osser & Persson 1984; Shioøtz & Csángó 1985; Osser & Persson 1989). On the basis of this, we recommend routine tests for *C trachomatis* in women ≤25 years of age having an abortion in the first trimester and prophylactic erythromycin in those positive. This regimen does not delay the abortion if *C. trachomatis* is identified by rapid immunological methods rather than by culture. To avoid reinfection, sexual partners ought to be identified and treated (Thelin *et al.* 1980; Weström 1982).

We found a high frequency of postabortal PID. This might be due to the relatively low sensitivity of the clinical diagnosis of acute PID (Jacobsen & Weström 1969; Caparro *et al.* 1978), the long postabortal follow-up and the involvement of many different general practitioners. But, in a double blind, controlled randomized study, such as ours, the uncertainty about the diagnosis of PID was the same in the treatment and placebo group. There is a need for further studies to develop more sensitive diagnostic tools in postabortal PID.

In our study, erythromycin prophylaxis in *C. trachomatis*-positive women significantly reduced the frequency of postabortal PID. It is noteworthy that only few women with postabortal PID were positive for *C trachomatis,* thus the prevention of postabortal PID is still a major challenge and further studies are needed.

Acknowledgments

The statistics are performed by guidance from The Danish Medical Research Council (j.nr. 5.52.19.28).

Abbott Laboratories A/S, Bygstubben 15, Trørød, 2950 Vedboek, supplied the antibiotics and placebo tablets.

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Received 29 March 1990
Resubmitted 19 March 1991
Accepted 19 January 1992

British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 439–440

CASE REPORT

Ovarian hyperstimulation syndrome and deep cerebral venous thrombosis

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Case report

A 29-year-old woman with amenorrhoea and polycystic ovaries attended for ovulation induction. Previous treatment had resulted in a triplet pregnancy complicated by ovarian hyperstimulation syndrome. That pregnancy had ended in a vaginal delivery at 24 weeks with one baby surviving. After clomiphene citrate treatment had failed, intramuscular injections of follicle stimulating hormone (FSH), 75 IU daily, were started. This dose was gradually increased in an attempt to avoid overstimulation. Follicle growth was monitored by vaginal ultrasonography. On 31.1.90, after 23 days of FSH, there were two large follicles (20 and 18 mm) and many smaller ones (all <14 mm); human chorionic gonadotrophin (hCG), 5000 units, was given.

The patient complained of abdominal swelling on 4.2.90. Deterioration with vomiting and headache led to hospital admission on 9.2.90. She had ascites with a packed cell volume (PCV) of 58% and a blood urea of 11·6 mmol/l. She received intravenous crystalloids and her condition improved although her abdomen became more distended. Fluid balance was monitored and urine output remained normal. A sudden left hemiparesis occurred on 12.2.90, at which time the PCV and blood urea were 44% and 4·4 mmol/l respectively. On 13.2.90 7·9 litres of fluid were removed by ultrasound directed paracentesis and ovarian cyst aspiration. Power returned rapidly to the patient's hand but a mild weakness of the hand and face persisted over the following days and was accompanied by episodic confusion. A left focal fit on 20.2.90 preceded further weakness and drowsiness. She became mute, with absent cough and gag reflexes and impaired swallow. Intra-arterial digital subtraction angiography (Fig. 1) showed thrombus in the right transverse sinus and occlusion of the internal cerebral vein and vein of Galen; intravenous heparin (30 000 units daily) was started. She was fed by nasogastric tube. On 24.2.90 a further 6·3 litres of fluid were removed by paracentesis and cyst aspiration. Despite a positive pregnancy test an intrauterine gestation sac was never seen on scan; bleeding started on 22.2.90 and serum levels of hCG dropped sharply. An early miscarriage was diagnosed and the anticoagulation therapy was changed to warfarin. The bilateral basal ganglia impairment gradually improved and the patient was discharged for rehabilitation on 15.3.90.

Follow-up 28 months later showed that her handwriting remained slightly impaired but she has returned to competitive sport.

Discussion

The ovarian hyperstimulation syndrome is a complication of superovulation treatment. Its pathogenesis is uncertain but a fluid shift from the vascular space explains the ovarian swelling, ascites, haemoconcentration and oliguria that occur. Thromboembolism is the most dangerous manifestation of the syndrome and there have been reports of cerebral infarction (Rizk *et al.* 1990) which was fatal in one patient (Mozes *et al.* 1965), deep venous thrombosis (Kaaja *et al.* 1989) and leg amputation (Mozes *et al.* 1965). This is the first report of deep cerebral venous thrombosis in association with the syndrome. Probably, extreme haemoconcentration, hyperviscosity and stasis predispose to thrombosis, but increased levels of coagulation factors and platelets have also been described (Phillips *et al.* 1975). In our patient, although the haematocrit was elevated initially (58%), it had returned to normal by the time hemiparesis occurred; thrombus may have been present already at the time of admission.

The ovarian hyperstimulation syndrome is a danger when large numbers of follicles grow in response to ovulation induction. An exaggerated response is particularly likely in women with polycystic ovaries; such women should be identified by pretreatment investigations and should receive a low dose of gonadotrophins. Unfortunately, even with an initial low dose, slowly increased, some women either fail to respond or develop too many follicles. If too many follicles grow, ovarian hyperstimulation may be prevented by withholding hCG or converting to management by in-vitro fertilization; experience with superovulation and oocyte collection suggests that fol-

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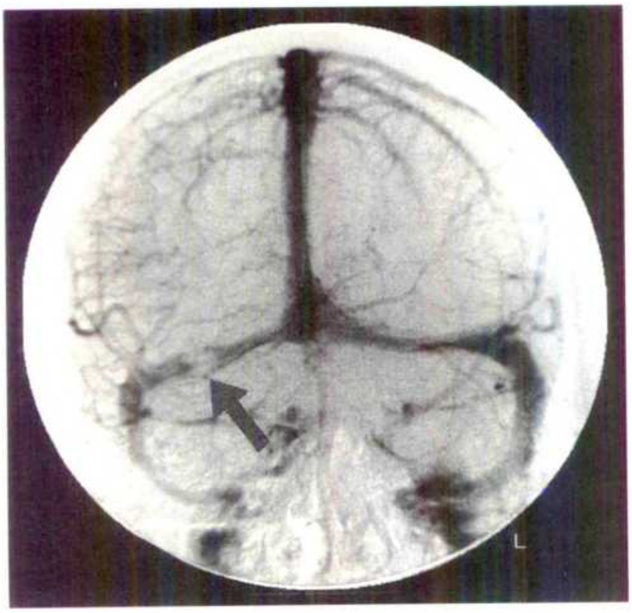

Fig. 1. Venous phase of cerebral digital subtraction study showing thrombus (filling defect arrowed) in the right transverse sinuse.

licle aspiration has a protective effect. Patients must be warned about the ovarian hyperstimulation syndrome before treatment is started and should be encouraged to return for review if significant abdominal swelling occurs. Vomiting is a particularly worrying symptom and may increase the risk of thromboembolism by exacerbating haemoconcentration.

Established severe ovarian hyperstimulation syndrome is treated with intravenous fluids to correct haemoconcentration and oliguria, although this may increase ascites. Previously, paracentesis was not recommended but is now gaining favour; not only does it relieve abdominal discomfort and respiratory embarrassment, but it may also promote a diuresis and accelerate resolution of the disease (Aboulghar *et al.* 1990). Therapeutic aspiration of ovarian luteal cysts has not been reported before. Past advocates of paracentesis have avoided ovarian puncture for fear of bleeding (Padilla *et al.* 1990), but this should not be a significant risk if ultrasound control is used.

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Received 28 October 1991
Accepted 21 November 1991

ERRATUM

FIGO staging for corpus cancer

We regret that there was a serious error in our report of the revised staging for corpus cancer published in our 1989 volume (*Br J Obstet Gynaecol* **96,** p. 889). Stage IIIB was incorrectly described and stage IIIC was omitted. The correct classification is as follows:

Stage		
IA	G123	Tumour limited to endometrium
IB	G123	Invasion to $<\frac{1}{2}$ myometrium
IC	G123	Invasion to $>\frac{1}{2}$ myometrium
IIA	G123	Endocervical glandular involvement only
IIB	G123	Cervical stromal invasion
IIIA	G123	Tumour invades serosa and/or adnexa and/or positive peritoneal cytology
IIIB	G123	Vaginal metastases
IIIC	G123	Metastases to pelvic and/or para-aortic lymph nodes
IVA	G123	Tumour invasion of bladder and/or bowel mucosa
IVB		Distant metastases including intra-abdominal and/or inguinal lymph nodes

We are grateful to Dr Tan Kok Hian of Singapore for drawing our attention to this error.

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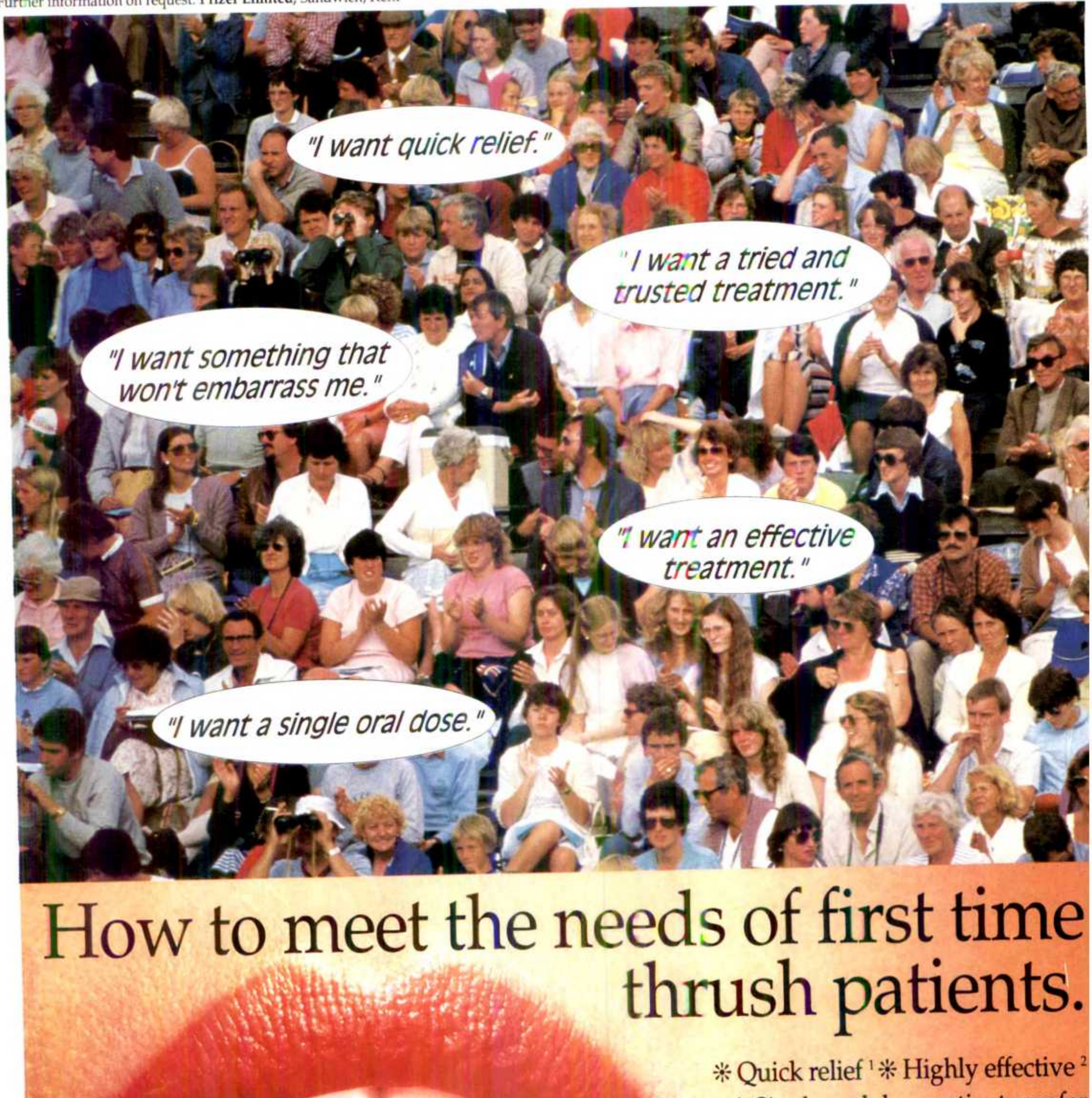
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British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 441–443

CORRESPONDENCE

The flying squad—an expensive and potentially dangerous practice in modern obstetrics

Dear Sir,

We read with interest the short communication by Trehan & Fergusson (1991) reviewing the flying squad in the West Lambeth area of London, and agree that this service has a limited role to play in an urban area. We feel, however, that these views cannot be applied to a flying squad serving a mixed urban and rural area. Over a 6 year period (1982–1987) the Chester flying squad has attended 54 calls and the largest proportion (44%) was to women who had or were about to give birth unsupervised at home. The squad team delivered two women with breach presentation, one twin pregnancy and two pregnancies by low cavity forceps. One placenta was removed manually. In addition three babies were intubated by the accompanying paediatrician and transferred safely to hospital. We do not subscribe to the view that the flying squad should be replaced by a mobile resusciation unit (Zorab & Basckett 1977). The best person to deal with an obstetric emergency in unfamiliar surroundings is an experienced obstetrician, not a paramedic with a training in obstetrical and gynarcological 'first aid' (Trehan & Fergusson 1991). A large number of calls to the flying squads are unjustified, but the squad still has an important role to play, especially in a mixed, or mainly rural area.

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The flying squad. Commentary

Dear Sir,

The commentary by Chamberlain & Pearce (1991) on the RCOG publication 'The future of Emergency Domiciliary Obstetric Services' draws attention to current problems and needs in this field.

The authors refer in particular to the need to negotiate for advanced training in resuscitation and transport of shocked patients by members of the Ambulance Service. In the fact that provision already exists for this development nationally, based on the experience of the South Glamorgan Emergency Domiciliary Obstetric Service which has been operational for 2 years and in which six training courses have been completed. With the support of the Joint Royal Colleges and Ambulance Services Liaison Committee the recently published new edition of *Ambulance Service Paramedic Training* (NHS Training Directorate 1991) incorporates a section on 'Emergency obstetrics and gynaecology'. This includes a unit on 'Care of the newborn' and recommends training in neonatal resuscitation to the standards defined in the RCOG publication *'Resuscitation of the Newborn (Part 1) Basic Resuscitation'* and the supporting video. This initiative provides the opportunity for all interested parties jointly to develop services according to local needs.

We note that in their survey of the Thames region Chamberlain & Pearce (1991) list six women who had a general anaesthetic for manual removal of the placenta at home. The need for such a hazardous procedure in modern practice suggest a need for critical review of individual cases and of the levels of anaesthetic expertise available.

The authors also recommend that 'Paramedical teams should therefore continue to carry blood and to administer it in specifically defined circumstances'. The decision to administer blood is essentially a medical prerogative and paramedics do not carry blood. Indeed, it would be to some degree a self-defeating exercise as the essential element of rapid response would be hampered should the team have to divert to the blood bank to collect donor blood. The need for blood transfusion at home is minimized by prompt effective treatment and use of plasma expanders. In our experience in the past most domiciliary blood transfusions could have been avoided without increasing the risk to the patient.

Our experiences of establishing a paramedic response, training and results will be published in due course.

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Dear Sir,

In their support of the RCOG Report (1990) to replace the obstetric flying squad with 'paramedics', Chamberlain & Pearce (1991) reviewed the flying squad service in Thames region and concluded that the flying squad is 'a hangover in the history of obstetrics.' We present data to illustrate our practice.

Aberdeen Maternity Hospital (AMH) provides a flying squad service to the whole of Grampian Region. This includes 12 peripheral general practitioner (GP) maternity units scattered for up to 80 miles from AMH. Between 1981 and 1990 there were 11 442 deliveries in these GP units and 461 deliveries outwith institution (patients' home, born before arrival). These represent 19% of the total deliveries (63 354) in Grampian. Excluding the calls from the two urban units (which are now closed) there were 141 flying squad calls (139 GP units, 2 patients home), a rate of 12 per 1000 peripheral deliveries. Overall 70% (97) of the calls were for retained placenta, 22% (33) for intrapartum problems and 7% for obstetric haemorrhage (8 antepartum, 1 postpartum). There were no calls for early pregnancy haemorrhage or gynaecological problems. Skilled obstetric procedures (nearly all under general anaesthesia) were carried out at the peripheral unit for 68% of the calls (60% manual removal of placenta, 8% others). Of the 23 patients who required blood or plasma expander transfusion, 20 had retained placenta. Overall 70% (96) patients were fit to continue their subsequent care at the peripheral unit and did not need to be transferred. There were two intrauterine deaths (placental abruption), one stillbirth (26 weeks) and no maternal deaths.

The RCOG recommendation 'is concerned only with true domiciliary services'. The flying squad in Thames region reflects a predominantly urban experience. The reduction, in Britain, from 60% deliveries in the domiciliary setting in the 1930s to <1% in the 1990s is the result of a shift in favour of deliveries in specialist hospitals and GP maternity units. In present day British obstetric practice, a more realistic assessment of the future of the flying squad may therefore be better achieved by assessing its utilization by GP units (especially peripheral) rather than by the domiciliary services taken in isolation.

Our data indicate a continued need for a service which will provide skilled obstetric and anaesthetic back-up rather than just resuscitation. Investing in training paramedics at present is unlikely to provide value for money. An increased emphasis on the content of hospital obstetric vocational training for general practice may prove more rewarding. However, in light of the changes in obstetric practice we, like ourselves, urge other regions to use the criteria laid out in the RCOG report as an impetus to audit the flying squad with regard to needs specific to their region. This would provide a more rational basis upon which to determine the future of flying squad in their region.

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Authors' reply

Dear Sir,

We are interested to read of colleagues' experiences in different parts of the United Kingdom and note how they vary. Our survey was of the Thames regions, a basically urban area, and what we found probably reflects other predominantly densely populated areas. We did not comment upon rural experience; it is interesting to note that the letters from Aberdeen and Wales, both regions with large rural populations, reflect opposing views. Professor Hibbard seems to have established an effective paramedical service while the Aberdeen group despatch a classical flying squad complete with anaesthetist; the Scottish scene may be more rural than the Welsh one.

Professor Hibbard has spent much time developing the South Glamorgan Emergency Domiciliary Obstetric Service and what he has written is very good sense. However, this system is by no means universally used throughout the country and indeed is still only being discussed in some ambulance areas. Whether paramedics should carry blood remains to be resolved; it is probable that in the next 10 years they will be doing it. We look forward to seeing Professor Hibbard's publication so that we can assess the results of the use of plasma expanders only by paramedics.

The experience of those running the flying squad in Chester does not substantially differ from the Thames regions, apart from deliveries in the home of women with complicated pregnancies and resuscitation of the newborn. When an obstetrician, particularly a less senior registrar, goes to the home of the patient in late labour, this is likely to be an entirely new experience for him. Unlike the paramedics, he has the choice of dealing with the problem in the home and it would be interesting to review the time sequence in breech presentations, twin pregnancies or instrumental deliveries.

Dr Chadha and colleagues' comments are very interesting. We wonder why there were no calls for early pregnancy haemorrhage or gynaecological problems. Could this possibly relate to who summons the flying squad in the Aberdeen area? There may be a devolvement of obstetrics back to community midwifery, with multiple small GP units or satellite hospitals carrying out deliveries; then a flying squad involving an obstetrician and an anaesthetist may still be justified. We will contend, however, that in the current scene and in urban areas, an efficient paramedical team bringing the women into hospital for proper therapy is more efficient. This still does not prevent the paramedics summoning an obstetrician or paediatrician as required but the basic primary resuscitation and transportation of the woman would be in their hands.

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The Stamey endoscopic bladder neck suspension: a clinical and urodynamic investigation, including actuarial follow-up over four years

Dear Sir,

Hilton & Mayne (1991) are to be congratulated for their very good article on the success of the Stamey procedure. In my opinion it very clearly identifies the place of this technique among the plethora of available options.

The surprising finding was that success rate in the over 65 year old was greater than in the younger patient. What is not clear from their article is whether the over 65 year olds had had less previous incontinence surgery. Their selection criteria were clear in that they only used this procedure in patients who had vaginal narrowing. However, in the young this may have been due to previous incontinence surgery, and in the older group it may have been due to vaginal atrophy.

A clarification of this point is important, as it is generally accepted that a past history of failed incontinence surgery is a poor prognostic feature.

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Hilton P. & Mayne C. J. (1991) The Stamey endoscopic bladder neck suspensions: a clinical and urodynamic investigation including actuarial follow-up over four years. *Br J Obstet Gynaecol* **98,** 1141–1149.

Authors' reply

Dear Sir,

We are very grateful to Mr Versi for his comments. Of the 25 women aged ≥65 years 19 had had a total of 30 previous unsuccessful incontinence operations; six had had no previous pelvic surgery whatever. Of the 75 women under 65 years of age, 46 had had a total of 59 previous unsuccessful incontinence operations; only eight had had no previous pelvic surgery whatever. Thus the older patients had in fact had slightly more previous unsuccessful surgery. Interestingly of those patients whose operations were unsuccessful from the outset, 13 were under 65 years of age, seven of these had had previous unsuccessful incontinence surgery, two had had previous hysterectomy and radiotherapy, and the other had had a simple hysterectomy. Four of the older patients were unsuccessful from the outset, of whom one had had previous unsuccessful incontinence surgery and two no previous pelvic surgery at all. Of the 15 patients whose operations failed at a later stage, 10 were under 65 years of age, seven had had previous unsuccessful incontinence surgery, one had previous radical hysterectomy, and two no surgery. Five of the older patients had later recurrences of whom one had had previous unsuccessful incontinence surgery, one hysterectomy and radiotherapy, one simple hysterectomy, and two no prior surgery. It would seem therefore that previous unsuccessful surgery mitigates against successful Stamey procedure in the young, but appears to be a rather less significant factor in the older patients. We do not have a clear explanation for these findings but would emphasize the conclusions made in the final paragraph of our paper, namely that '. . . the Stamey endoscopic bladder neck suspension has an important role in the management of women with complex stress incontinence, and is particularly appropriate in elderly patients, and in those with multiple previous unsuccessful operations . . . '. We are much less happy about its use in younger patients, particularly those with multiple previous unsuccessful operations.

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Colposcopically directed punch biopsy: a potentially misleading investigation

Dear Sir,

I was interested to read the study of Buxton *et al.* (1991) concerning the limitations of colposcopically directed punch biopsy. They found that 132 (54%) of the results of punch biopsy did not agree with subsequent loop diathermy biopsy. This prompted the authors to cast considerable doubt on the use of punch biopsy findings as an endpoint. However, if the study design and the clinical implications of these discrepancies are considered it is possible to be less pessimistic about punch biopsy.

The discrepancies can be divided into five groups: (1) In 70 cases the punch biopsy showed a more severe lesion than the loop biopsy. This suggests that the taking of a punch biopsy had a direct effect on loop biopsy findings. Therefore the disagreement in histology may be caused by the design of the study rather than because of a problem with the punch biopsy. (2) In 16 cases the punch biopsy showed CIN 2 and the loop biopsy showed CIN 3. In most clinics the treatment of CIN 2 and 3 is identical so that little clinical significance can be attached to the discrepancy. (3) In three cases the punch biopsy showed CIN 2 or 3 while the loop biopsy showed adenocarcinoma *in situ*. It is probably not reasonable to expect a colposcopically directed punch biopsy to pick up adenocarcinoma *in situ* since it is principally aimed to diagnose CIN. This finding does of course lend support to a preference for treatment by excision rather than local destructive techniques. (4) In one case the punch biopsy showed CIN 3 but the loop showed stage Ia1 invasive cancer. This is of course worrying but there was an interval between the two biopsies and the disease could have progressed within that time. (5) In the remaining 42 cases (17% of the total group) the punch biopsy underestimated the loop biopsy in such a way that treatment or follow up might have been different. Again there could be some effect due to disease progression between the biopsies or the effect of punch biopsy on subsequent loop biopsy and, as the authors state, observer variation in grading the lesions was not considered. However, in 19 of these cases there was CIN 3 on loop biopsy but CIN 1 or less on punch biopsy and in 10 cases there was CIN 2 on loop biopsy but no evidence of CIN on punch biopsy. It is difficult to explain these 29 cases (12% of the total group) without doubting the punch biopsy.

This paper suggests that there are limitations to punch biopsy but the problem has perhaps been overstated when the clinical implications and effects of study design are considered.

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References

Buxton E. J., Luesley D. M., Shafi M. I. & Rollason T. (1991) Colpospically directed biopsy: a potentially misleading investigation. *Br J Obstet Gynaecol* **98,** 1273-1276.

Author's reply

Dear Sir,

We read the letter Mr A. R. Beeby with interest, unfortunately it would appear that he has missed the point of our study.

Whilst we would agree that in the majority of cases, if it is assumed that all patients with any degree of dysplasia are to be treated, the discrepancy between punch biopsy and that of the excised transformation zone is of little clinical relevance, there remains a substantial group of cases in which under-treatment of a high grade lesion could occur if reliance on the punch biopsy result was absolute. As we stated in our discussion, given the short interval between punch biopsy and loop excision, we feel that disease progression is an unlikely explanation for this phenomenon. We therefore, stand by our comment that this finding has important implications for patient management.

Our study confirmed the inaccuracy of punch biopsy. Although the clinical implications are important, of equal significance is the effect this will have on the results of any study of preinvasive disease which relies on punch biopsy to establish lesion grade. Since punch biopsy has potential not only to underestimate lesion severity but also to influence the course of the disease process, our findings mandate the development of more accurate non-invasive methods of establishing lesion grade or the use of more appropriate control groups in such studies.

Finally we agree with Mr Beeby that in those cases where punch biopsy overestimated lesion severity this may be due to the effect of the biopsy on the biology of the disease or may reflect complete removal of small lesions since there was a direct relation between this phenomenon and lesion size. These points were covered in our discussion.

Our findings lend further support to the growing trend towards the use of excisional rather than destructive techniques in the treatment of cervical intraepithelial neoplasia.

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British Journal of Obstetrics and Gynaecology
May 1992, Vol. 99, pp. 444

BOOK REVIEWS

Scientific Foundations of Obstetrics and Gynaecology edited by Elliot Philipp & Marcus Setchell with Jean Ginsberg. Butterworth Heinemann, Oxford, 1991, 764 pages, with figures and tables, £125

The fourth edition of this book has appeared five years after the previous one. Of the original three editors only Elliot Philipp remains, and he is joined by Marcus Setchell and Jean Ginsberg. The new edition has many more pages but fewer chapters, of which 12 are new. Some topics have been dropped and others amalgamated, and generally this is an improvement; for example the four chapters dealing with carbohydrate, lipid and protein metabolism have been combined into one on intermediary metabolism which gives a more coherent account and avoids repetition. There are 91 authors of whom 51 are new.

Thus the editors have taken the opportunity to reform the book radically. Has this been successful? Certainly there are improvements, especially by Jean Ginsberg in the nutrition, endrocrinology and metabolism section. The chapters on genetics, the menstrual cycle, and ovulation, fertilization, embryo cleavage and implantation have been expanded in keeping with the increase of knowledge in these fields. Other changes are not so successful. One of the problems is that clinicians sometimes write about disease instead of physiology; for example the section on the uterine tube has 13 photographs of hydrosalpinx. The chapter on fetal oxygenation and circulation is especially disappointing, since it seems to be a summary only of the authors' research on intrauterine growth retardation, with a lack of basic description of the anatomy of the fetal circulation and oxygen-dissociation curves. The corresponding chapters in the previous edition were much better.

This book will be useful to senior and to junior obstetricians and gynaecologists, especially those juniors about to sit the first part of the MRCOG. However the price is a deterrent, and the MRCOG candidate may prefer to read a shorter and cheaper book and augment his knowledge by reference to Scientific Foundations in the library. The publishers should look for ways to reduce the price, perhaps by omitting some topics, or producing a paperback edition.

John M. Grant

The Woman's Booke—Embryology, Obstetrics and Gynaecology Through Four Centuries. An illustrated and annotated catalogue of rare books in the Swedish Medical Society. Compiled by Ove Hagelin. From booksellers or direct from Hagelin Antikvariat, Box 3321, 10366 Stockholm, Sweden. 176 pages fully illustrated, 396SEK

Did you know that the eighth child—and fifth son—of Sir J. Y. Simpson was named for Professor Magnus Retzius? Professor Retzius was Head of Obstetrics and Gynaecology at the Karolinska Instituet at the time and a close friend of the great J.Y.S.

Four stages of nymphomania were described by M. Bienville in 1775—have things changed or haven't they?

Mlle Louise Bourgeois (Mme Boursier) practised midwifery among the poor people of Paris after receiving instruction in the art by her husband, who was a skilled barber-surgeon. Mlle Bourgeois was the first midwife to write and have published a handbook for the use of others.

These and many more fascinating facts are contained in this remarkable 'catalogue' of treasures.

In 1986 Ove Hagelin, an antiquarian book dealer was asked by Dr Goran Falkenberg, librarian to the Swedish Society of Medicine (Svenska Lakare Sallskapets/SLS) to catalogue the library. Many many treasures were found.

The SLS were determined to make details of this unique collection available to a wider audience. Funded by a generous grant from the Knut and Alice Wallenberg Foundation, Ove Hagelin set about this task. The Woman's Booke is the second compilation in the planned series.

He has listed the important books in chronological order, reproducing and translating the title pages and some of the more remarkable illustrations by each author. There is also a brief history of each author and his place in medical history, backed by references. All this has been completed in impeccable English—I'm glad to say.

Most of us will not be fortunate enough to touch or even to see the important historical literature of our profession. This book and its companions from the SLS are an excellent substitute, and will give much pleasure to the 'occasional' medical historian.

Patricia Last

Books received some of which may be reviewed at a later date

The Right to Choose. Pioneers in Women's Health and Family Planning by Perdita Huston. Earthscan Publications Ltd, published in association with the IPPF, 1992, 193 pages, £9.95

The Extracellular Matrix of the Uterus, Cervix and Fetal Membranes: Synthesis, Degradation and Hormonal Regulation edited by Phyllis C. Leppert & J. Frederick Woessner Jr. Perinatology Press, Ithaca, New York 1991, 284 pages with figures and tables US$110.00 (prepaid discount price $88.00)

Pre-Eclampsia: The Facts by Chris Redman & Isabel Walker. Oxford University Press, Oxford, New York, Tokyo 1992, 197 pages. Paperback £8.99

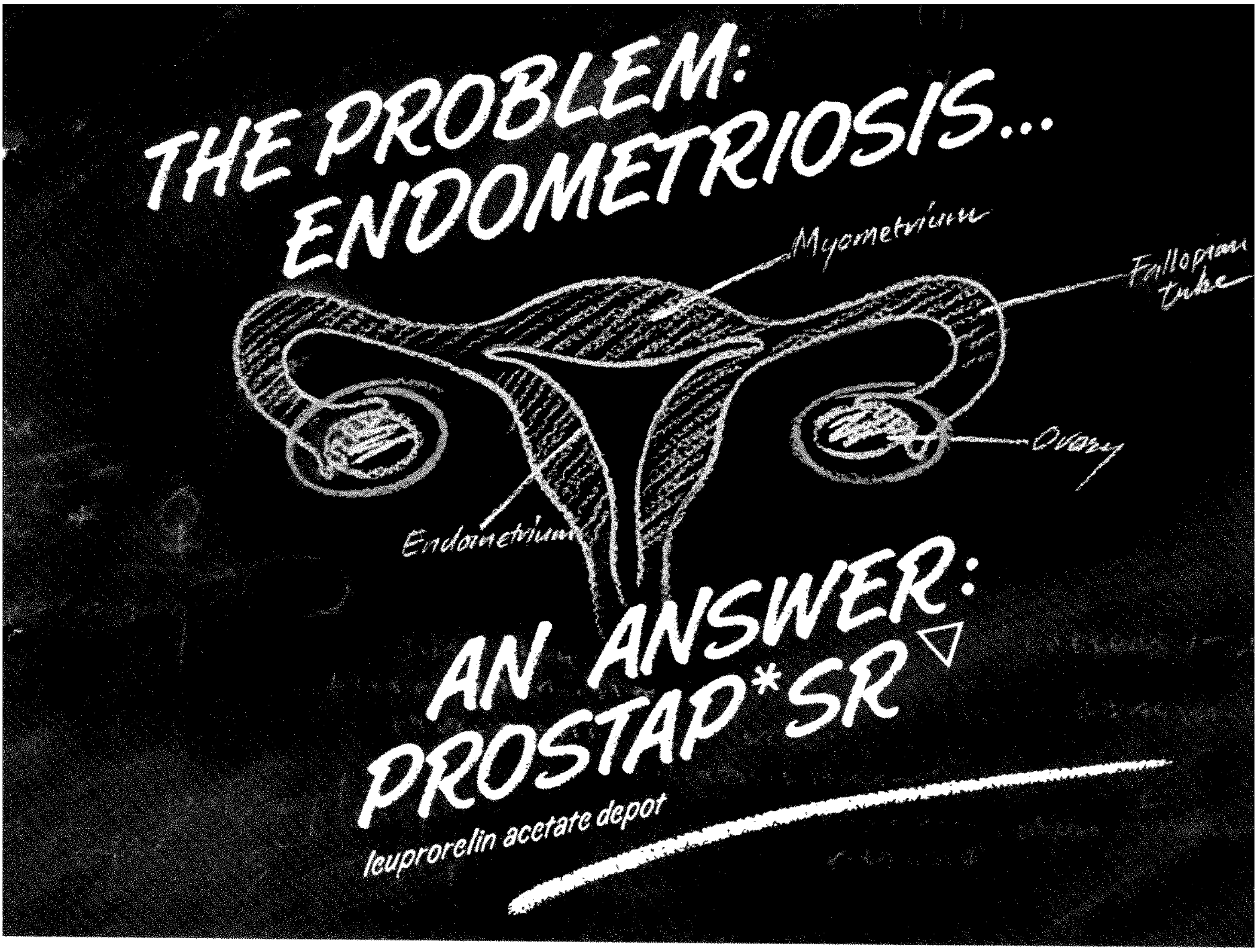
Obstetrics and Gynaecology for Postgraduates Vol 1 edited by S. S. Ratnam, K. Bhasker Rao & S. Arulkumaran. Orient Longman, Madras, 1992, 430 pages with figures and tables, Rs325.00

Exercise & Physiotherapy in the Prevention and Treatment of Osteoporosis No 8 in a series of Information Booklets published by The Osteoporosis Society, 1992, 35 pages illustrated. Available from The National Osteoporosis Society, PO Box 10, Radstock, Bath BA3 3YB. £2.50

Proceedings and Symposiums

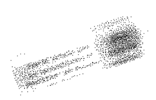
Placenta: Basic Research for Clinical Application International Conference on Placenta held in Tokyo in 1990 edited by H. Soma. Karger, Basel, 1991, 214 pages with figures and tables, SFr. 230 DM275.00, £100.00/US$184.00

AIDS and Human Reproduction First International Symposium on AIDS and Reproduction, Genoa December 1990 edited by F. Melica Karger, Basel, 1992, 196 pages, with figures and tables, SFr 169, DM202.00, £73.50, US$135.25



Effective GnRH agonist therapy for endometriosis,[1,2] from a simple monthly subcutaneous injection.

A very fine suspension, given through a fine gauge needle, offers patient acceptability and ease of administration in clinic, outpatient or domiciliary use.



PROSTAP* SR ▼

leuprorelin acetate depot

A Logical Approach to Endometriosis

REFERENCES

1.Dlugi AM *et al* Fertility & Sterility 1990: **54** (3) 419-427. (RJG33) **2.** Adashi E *et al.* Data on File, Lederle Laboratories.

ABBREVIATED PRESCRIBING INFORMATION Before prescribing Prostap SR, please refer to full data sheet.

Presentation: Vials containing 3.75mg leuprorelin acetate as microcapsule powder. For reconstitution with Sterile Vehicle, presented in a prefilled syringe. **Indications:** The management of endometriosis, including pain relief and reduction of endometriotic lesions. **Dosage:** 3.75mg administered as a single subcutaneous or intramuscular injection every month for a maximum period of 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle. **Contraindications:** Lactation, pregnancy, undiagnosed abnormal vaginal bleeding. **Warnings:** Whilst ovulation is usually inhibited during therapy, contraception is not ensured, therefore, patients should use non-hormonal methods of contraception. During the early phase of therapy, sex steroids temporarily rise, possibly leading to an increase in symptoms. This, however, dissipates with continued therapy.

Precautions, side-effects: The induced hypo-oestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. However, during one six-month treatment period, this bone loss should not be important. The generally accepted level of bone loss with LHRH analogues such as Prostap is 5%. For patients with major risk factors for decreased bone mineral content, Prostap therapy may pose an additional risk. Other side effects reported are mainly those related to hypo-oestrogenism; hot flushes, headaches, emotional lability, and vaginal dryness. **Legal category:** POM. **Package Quantities:** Vials containing 3.75mg leuprorelin acetate as microcapsule powder. Prefilled syringes containing 2ml of sterile vehicle. **Basic NHS cost:** £125.40. **Product Licence Numbers:** Prostap SR Powder 3.75mg vials; PL0095/0218. Sterile vehicle prefilled syringes PL0095/0220. Cyanamid of Great Britain.

For further information, see data sheet.

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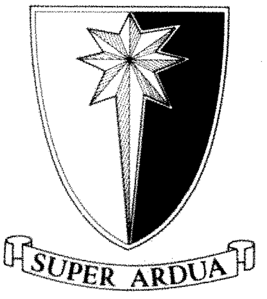
Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London

Volume 99, Number 6, June 1992 BJOGAS 99(6) 445–536 1992 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

Edited by David B. Paintin



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6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

50 Years Experience

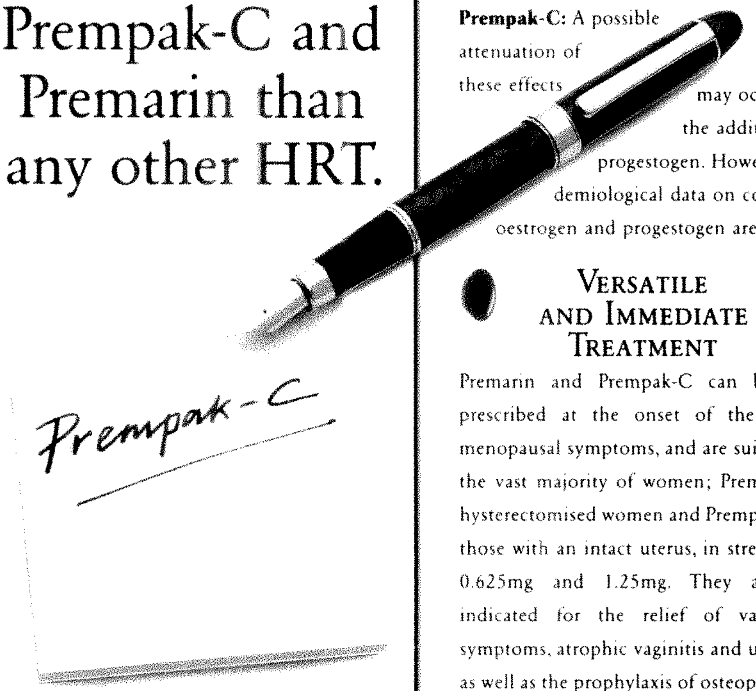
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

Long Term Safety - Breast Cancer?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

Prophylaxis of Osteoporosis

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



Reducing Cardiovascular Disease Risks

Premarin: A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users. The most common form of oestrogen used in all these studies was conjugated oestrogen, i.e. Premarin.

Prempak-C: A possible attenuation of these effects may occur with the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited.

Versatile and Immediate Treatment

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women; Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625mg and 1.25mg. They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk.

Cost Effective

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1.84 and Prempak-C costs £4.06, for 28 days of therapy.[7]

PREMPAK-C

PREMARIN

Abbreviated Prescribing Information

PREMARIN **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily. Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential.
CONTRA-INDICATIONS: Known or suspected pregnancy and during lactation. History of known or suspected cancer of the breast. Oestrogen dependent neoplasia. Undiagnosed abnormal genital bleeding. Active thrombophlebitis or thromboembolic disorders. Acute or chronic liver disease. Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease.
WARNINGS AND PRECAUTIONS: Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship. It is not known whether concurrent progestogen influences this risk. The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma. Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction. Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop. Certain endocrine and liver function tests may be affected. Rarely idiosyncratic hypertension may occur. Discontinue treatment prior to surgery or prolonged immobilisation. Gallbladder disease. Insulin requirements may be altered. Premarin is not an oral contraceptive.
SIDE EFFECTS: The following have been reported with oestrogen therapy: premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps.
PRODUCT LICENCE NUMBERS: Premarin 0.625mg PL0011/0165 Premarin 1.25mg PL0011/0166 Premarin 2.5mg PL0011/0167. **BASIC NHS PRICE:** Premarin 0.625mg £1.84 (28 days). For full prescribing information please refer to data sheet.

PREMPAK-C **USES:** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily and one norgestrel 0.15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy.
CONTRA-INDICATIONS: As for Premarin.
WARNINGS AND PRECAUTIONS: As for Premarin. Prempak-C is not an oral contraceptive.
SIDE EFFECTS: As for Premarin. Breakthrough bleeding and spotting. Change in menstrual flow, dysmenorrhoea, amenorrhoea.
PRODUCT LICENCE NUMBERS: Prempak-C 0.625mg PL0011/0161 Prempak-C 1.25mg PL0011/0162.
BASIC NHS PRICE: £4.06 (28 days). For full prescribing information please refer to data sheet.
REFERENCES 1 Dupont W.D and Page D.L. (1991) Arch. Int. Med. 151, 67-72. 2 Lindsay R. et al. (1984) Obstet. Gynecol. 63, 759-763. 3 Kiel D.P. et al. (1987) NEJM, 317, 1169-1174. 4 Ross R.K. et al. (1989) Lancet, 1, 505. 5 Stampfer M.J. and Colditz G.A. (1991) Prev. Med, 20 47-63. 5 Stampfer M.J. et al. (1991) NEJM, 325, 756-762. 7 MIMs June 1992.
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PREMARIN*
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

PREMPAK-C*
(Conjugated Oestrogens + Norgestrel)

British Journal of Obstetrics and Gynaecology

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British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 445–451

COMMENTARIES

The House of Commons Health Committee Report on the Maternity Services. A personal view

The House of Commons Health Committee report (second part, dealing with antenatal, intrapartum and postnatal care) was printed on the 13 February 1992 and published on Wednesday 4 March 1992. The recommendations of the Committee are now a matter of public record. Most obstetricians will have views about them, but are perhaps unaware of how they came about. Certainly before I became an advisor to the committee, I had little insight into how the democratic process works in relation to this type of report.

The Committee represents the members of the House of Commons under standing order number 130 and is empowered to examine the expenditure, administration and policy of the Department of Health, associated public bodies and similar matters, within the United Kingdom. It comprised 11 MPs, with cross party representation; the chairman was Nicholas Winterton, a Conservative. The other members were nominated because of an interest in the Health Service: prominent amongst them was Audrey Wise, a Labour MP with links to the Royal College of Midwives. The Committee is evenly balanced on party lines, with the Chairman having the casting vote which by tradition he casts in favour of the party in office.

Selection of advisors is within the remit of the Committee; there appears to be no set rules about how many there should be or how they are selected. I was apparently recommended by a previous advisor to the Committee, Professor Richard Beard. At our first meeting, a major topic of interest for the advisors was to discover why we had been selected. Each advisor had to submit a curriculum vitae and be interviewed by the Committee for suitability. For those not familiar with the impressive interior of the House of Commons, to be ushered by a man in a tail coat and a white bow tie into a sort of dock to be quizzed by MPs had an effect similar to being interviewed for a consultant post. For this report, there were five advisors: Dr Naren Patel (secretary of the RCOG), Professor Osmund Reynolds (a paediatrician, University College Hospital, London), Dr Luke Zander (senior lecturer in general practice, St Thomas's Hospital, London), Mrs Rosemary Jenkins (Royal College of Midwives), Caroline Flint (an independent midwife), and myself.

Once selected, we had to recommend a series of witnesses who might be asked to present evidence, either written or in person, depending on the decision of the MPs. The organization rested in the hands of the Clerk to the Committee, a senior civil servant. Initially this was Ms Helen Irwin but half way through she moved to foreign affairs, to be replaced by Mr Paul Evans. The Clerk has a position of considerable influence, not only responsible for calling evidence, but for drafting the actual report.

The evidence received is the key to the final report. Issues are only likely to be included if they are submitted to the Committee. Submissions came thick and fast once the various pressure groups became aware of the Committee's operation; over 400 submissions both solicited and spontaneous had been received by the time the Committee reported. All submissions are circulated to MPs and advisors, even letters from individuals. In many senses this is true democracy in action and the individual can certainly make an impact if his/her submission is effective. On the other hand, it is not a systematic enquiry and in no way is the evidence collected a scientific or representative survey. In the latest enquiry, a large majority of the individual submissions were from proponents of radical midwifery or from individuals or organizations dissatisfied with the current operation of the maternity services. Some of the personal appearances were requested by the MPs. For example, a woman who had difficulty in organizing a home birth complained to her MP Mr David Hinchcliffe, who as a member of the Committee arranged for her to address it; her correspondence was also submitted in evidence. A group of women who had been more successful in achieving home births were invited along by Luke Zander, their general practitioner. One woman emphasized her message by breast feeding while addressing the Committee. About 40 to 50 spectators are allowed in to witness the public deliberations of the Committee; these were predominantly midwives and lay maternity activists who supported the more radical proposals with murmurs of approval and sometimes applause. Suggestions from the RCOG that hospital births are safer were met by a mass intake of breath and head shaking.

As an advisor I was not required to attend all or even any of the meetings because I was provided with a verbatim transcript within a week from which to work. However, I attended about half and found it important in order to judge the mood of the Committee in relation to writing the report later. I was surprised to find that the advisors do the actual writing; it is welded together 'into a seamless whole' by the Clerk. The MPs, however, have the final say as to whether any part is subsequently included in the final report. It was therefore pointless to write anything which was clearly out of sympathy with the feelings of the MPs, and the Clerk would rewrite anything he thought too partisan in a way he thought would be acceptable to them.

One of the duties of the advisors is to suggest questions to be asked at forthcoming oral sessions. This was sometimes a useful way to make witnesses address one's own concerns. However, the MPs did the actual questioning and therefore often the discussion took a completely different direction to the one anticipated, particularly if the witnesses gave an unexpected answer.

The MPs also made a number of visits to maternity units around the UK, in Holland and Sweden. The advisors were invited to travel with them. However, they were organized at relatively short notice which largely precluded the medical advisors from travelling although the midwives seemed to have more flexible timetables.

Towards the end of the enquiry (which lasted about 10 months) there were a number of long drafting meetings where the contributions of the various advisors were assembled together. Conversations sometimes became heated but were handled skilfully by the Clerk and it is a tribute to Paul Evans that we were still all talking to one another at the end. The final meetings were also attended by two or three of the more involved MPs. Some of my personal concerns, such as our heavy reliance on overseas doctors for resident obstetric cover (almost 60% of resident registrars are not UK graduates), disappeared completely. Others, such as the number of obstetricians per 1000 births, were cleverly boomeranged by the Clerk, who discovered that the examples quoted in evidence (one per 1054 births in Plymouth UK, one per 544 births in Scotland and one per 163 births in Newcastle, New South Wales) were inversely related to perinatal mortality rates (6·8 per 1000 in Plymouth, 8·7 in Scotland and 10 in Newcastle). Still others, for example a contribution on medicolegal aspects, were printed almost unchanged.

At the final meeting, all the MPs were present and went through the report line by line. They changed words or paragraphs, sometimes with a dramatic effect on the meaning, until they were happy it expressed their opinion, and not ours.

The report as published is an account of a strong current of public opinion, as seen through the eyes of the public's elected representatives. It is not a scientific but a political document. It has a stimulant rather than a prescriptive effect. The Government is obliged to reply to it, but not necessarily to respond by action. Nonetheless, such a report can have a significant effect on policy and as such it behoves all of us to consider its recommendations carefully.

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British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 446–448

Non-invasive first trimester antenatal diagnosis

The present techniques offering antenatal diagnosis all have been confined to women who have reason to think they are at a risk of greater than approximately 1 in 100 of having a severely handicapped child: amniocentesis (which is offered late in pregnancy), chorion villus sampling (which has a risk of miscarriage) and pre-implantation diagnosis (which is experimental and very expensive). We outline the current position for non-invasive procedures now under study which might allow antenatal diagnosis to be offered for all pregnancies during first trimester. The possibility of obtaining trophoblast cells from the maternal circulation appears to have particular likelihood of success.

At present, fetal diagnosis for severe abnormality due to chromosomal, gentic or structural abnormality uses ultrasound, maternal biochemical screening, chorion villus sampling (CVS) and amniocentesis.

Both chromosome and single gene disorders can usually be diagnosed in the first trimester using CVS. There is now evidence from the MRC Working Party on the Evaluation of Chorion Villus Sampling (1991) that CVS is not as safe as amniocentesis. Additionally, Firth *et al.* (1991) have recently reported a possible association between CVS and fetal limb abnormalities. Placental mosaicism is found eight times more commonly in chorion samples than at second trimester amniocentesis, which could result in misdiagnosis leading to inappropriate termination of pregnancy.

Amniocentesis can now be performed as early as 12 weeks, but is most commonly performed at 16 to 18 weeks. It carries a lower risk of miscarriage, but if termination is requested following the diagnosis, it has to be carried out late in second trimester, which is unacceptable to many pregnant women. Although earlier amniocentesis is now performed in several centres on a research basis, it is not yet clear whether there is a risk to the fetus.

Both pre-implantation (Coutelle *et al.* 1989; Handyside *et al.* 1990) and pre-fertilization (Verlinsky *et al.* 1989; Monk & Holding 1990) diagnoses will soon be available coupled with in vitro fertilization, but such techniques are experimental, associated with failure to obtain viable pregnancies and with great cost in professional and patient time.

Community genetics testing for common autosomal recessive diseases, using DNA technology, is now being studied in pilot programmes for cystic fibrosis in the UK (Watson *et al.* 1991), and has been applied for thalassaemia in Cyprus, Sardinia and other Mediterranean regions and for at risk groups in England (Modell 1989) and for Tay-Sachs disease among some Jewish groups (Kaback 1977). Through community testing, many couples who have no personal experience of the inherited disease may none the less find they are at risk, and would welcome an antenatal diagnostic procedure which poses the minimum inconvenience to the partners and the minimum risk to the fetus. (Such developments would also, of course, be welcomed by couples at high risk who are identified by previous affected children, as well as by those offering antenatal diagnosis services.)

For a procedure to be acceptable, it is necessary that it should be of no or low risk to a viable pregnancy. It is best if it is offered early in the pregnancy, so that if a termination is requested it can be performed during first trimester. It should have a high specificity and accuracy, should not require a high rate of resampling, should be easy to administer and to understand. The cost to benefit ratio should be high, which in practice means that the cost should be very low, as many people may request testing. The technique should be applicable to many conditions, with only a variation in the end point testing required for changing the object of the test.

Two procedures have been proposed which meet these criteria for the most common situations, chromosomal aneuploidies (such as Down's syndrome) and single gene disorders such as cystic fibrosis. One involves the isolation of fetal cells from the maternal circulation. The second involves the isolation of fetal cells from the cervix as reported by Griffith-Jones *et al* in this issue of the Journal (p. 508).

We outline the advantages and disadvantages of each procedure, and some questions which must be answered before the procedures can be used widely.

The fate of the trophoblast during fetal development

After implantation, the cyto- and syncytiotrophoblast develop and surround the inner cell mass. The chorionic villi formed by the syncytiotrophoblast are a particularly easy tissue to use for DNA diagnosis, as the syncytial cells are rich in DNA and low in nucleases; however, they are more difficult to use for karyotyping, as they enter cell division only after considerable *in-vitro* manipulation.

At approximately 4 weeks, the chorionic villi are no longer maintained on the outer surface, and a smooth chorion is formed. Within the placenta, the villi become more specialized and provide the interface between the maternal and fetal circulations; it is this tissue that is sampled in CVS. The villi that are lost from most of the surface of the chorion laeve can be found in blood samples from the uterine veins during pregnancy, and also in the cervical sump. It is clear that these villous fragments retain characteristic morphology and cell surface antigens, but are often fragmented and may contain dead or dying cells which are pyknotic and may be unable to divide.

Isolation of fetal cells from the maternal circulation

A recent review has summarized attempts to obtain fetal cells from the maternal circulation (Adinolfi 1991). It is clear that there are at least two types of fetal cell which can be isolated from maternal blood, fetal blood cells (for the most part, either erythroblasts or lymphocytes) and fetal trophoblast. In almost all series, contamination with maternal cells was noted, but not quantified. Recent analysis has used gene amplification (using polymerase chain reaction), often with Y-chromosome specific gene probes. These polymerase chain reaction techniques are exquisitely sensitive, and are very difficult to quantitate; they have usually demonstrated a small number of fetal cells from a male fetus in the presence of a much larger number of maternal cells. Sometimes the cells are analysed without further purification from a whole blood sample, though they may be flow-sorted using an antibody to a fetal antigen (Bruch *et al.* 1991); unfortunately, such antigens are rarely completely specific.

It would be anticipated that any study based on isolating fetal trophoblasts would be far more specific than any based on fetal lymphocytes or erythroblasts, as there are no normal cells similar to trophoblasts in the maternal circulation. Therefore, it is not surprising that the most convincing study of isolation of fetal cells used anti-trophoblast monoclonal antibodies (Mueller *et al.* 1990); although full data on the ratio of fetal to maternal cells were not given, the use of antibody-coated magnetic beads should permit recycling, and the technology invites the development of more specific antibodies which could lead to the isolation of a pure fetal cell fraction.

Until recently, a full chromosome analysis was needed to identify a fetus affected by Down's syndrome or other aneuploidies, but now fluorescent *in situ* hybridization (FISH) using chromosome specific DNA probes (chromosome painting) on interphase cells can identify trisomies with accuracy (Lichter *et al.* 1990). At present it is only possible to do this for a limited number of chromosome disorders and thus to identify only a proportion of possible aneuploidies in any one sample. However, it is possible that for antenatal screening of the entire population it would be sufficient to screen for Down's syndrome and sex chromosome aneuploidies, as these are the most significant causes of post-natal morbidity. It should be noted that preconception screening of women using similar techniques will also identify those at risk of having children affected by unbalanced translocations.

It is surprising how few studies have addressed the following questions: What is the precise fetal cell type that is obtained for study? Is it viable and can it yield a conventional karyotype? What ratio of fetal to maternal cells can be achieved? What purity is required for accurate analysis using gene amplification? Are the fetal cells suitable for single gene analysis using the polymerase chain reaction, or for interphase *in situ* fluorescent analysis for aneuploidy? Precisely when do the fetal cells (chorion- or blood-derived) appear in the maternal circulation during pregnancy? Are there any fetal cells remaining in the maternal circulation from a previous pregnancy after parturition, and how long do they persist? What is the variability for all these factors from one pregnancy to another? These critical questions have to be addressed before it will be possible to apply fetal cell isolation from the maternal circulation in obstetric practice.

Isolation of fetal cells from the cervix

Since the trophoblast degenerates into the lumen of the uterus, and many cells appear to be shed through the cervix, it is possible that one might isolate fetal cells from either cervical smears or mucus plug biopsies. There are remarkably few reports of attempts to obtain fetal cells from this site. Rhine *et al.* (1977) studied the cells from cervical mucus, and he demonstrated Y-body fluorescence in the cells which were identified without a single sex determination error. In this issue of the Journal (p. 508) Griffith-Jones *et al.* report a further attempt to retrieve cells from the cervix, and to use these for DNA analysis with Y-specific DNA gene amplification.

We have recently tested a series of 24 women prior to elective first trimester termination of pregnancy for fetal cells in the cervical exudate. The test used polymerase chain reaction gene amplification of sequences specific to the Y-chromosome on DNA from cells obtained from both the cervical smears and mucus plug biopsies prior to termination. The data were compared with the fetal sex as determined by Y-sequence polymerase chain reaction and by karyotyping on cells from fetal parts obtained after the termination. Unlike the report in this issue (p. 508), we were not able to make correct predictions; only 4 of 13 male pregnancies were predicted from the cervical smear and 7 by mucus plug biopsy. Because we misdiagnosed some female pregnancies as well, we also believe that the presence of sperm from a partner after intercourse (50% of such sperm would contain a Y-chromosome) may be a problem. We did not regard it as ethical to ask whether intercourse had taken place within a few days of termination. It is not known how long sperm DNA can persist in the vagina and cervix (non-viable sperm can still give DNA which will score 'positive' in this assay).

We are not sure why our data differed from those reported by Griffith-Jones *et al.* in this issue (p. 508), but this is probably due to changes in isolation and lysis procedures. It is important that their very encouraging data reporting accurate fetal sexing using cervical cell samples should be confirmed and extended to study fetal risk and timing. We are sure the authors (and others) will report the results of such experiments shortly. It is possible that fetal cells can be separated from cervical exudate by flow sorting, or other immunological procedures such as those used by Mueller *et al.* (1990), although it will always be difficult to exclude the possibility of sperm contamination by adsorbtion, or that differential lysis could be employed to purify fetal DNA.

It is clear that fetal trophoblasts can be isolated from maternal blood, or from cervical exudate in yields sufficient for DNA testing and for interphase karyotyping. Both techniques give encouraging results, although many experiments to define the factors involved in each approach remain to be done. Isolation of fetal cells from blood poses problems of purification; the fetal cells are present in very small amounts. The cervical approach may place the fetus at risk of infection, and we see no easy way to circumvent the problem of sperm contamination of cervical fluids. Therefore, we believe that it is more likely that maternal blood will be the source of fetal trophoblast for DNA-based diagnosis in future, provided that antibodies of sufficient specificity can be prepared and that the kinetics and quantitation of the system show that it is generally applicable and reproducible, although there may be an application for cervical cell testing to obtain fetal sex in the case of sex-linked disease.

Acknowledgments

We thank the North West Thames Regional Health Authority for a grant to carry out this research, and Carolyn Williams (Director, NWT Regional DNA Laboratory, St. Mary's Hospital Medical School) for encouragement and support.

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British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 449–451

Amnioinfusion: a question of benefits and risks

In recent years, several reports have appeared describing the use of amnioinfusion antenatally and during labour. This procedure involves the infusion of saline solution into the amniotic cavity transabdominally, or by means of a transcervical catheter, with the objective of augmenting amniotic fluid volume or diluting meconium.

The incorporation of new clinical techniques into routine practice constitutes a complex ethical problem. Unlike new medicines, clinical procedures are not subject to statutory assessment processes before they are made available for general use. Clinicians are free to decide for themselves whether the benefits of a new technique are likely to outweigh any possible adverse effects. What should the guidelines for such decisions be?

The potential benefits of a procedure are usually clearly defined. Certain possible adverse effects may be predicted and therefore measured. In addition, however, allowance must be made for the possibility of adverse effects which have not been predicted, and therefore have not been included as outcome measures in any clinical trials. Interventions during labour, in particular, may interfere with physiological and psychological processes in ways which are difficult to predict or measure. Because of such unknown quantities, it is important that before any intervention can be recommended for general use, convincing evidence of beneficial effects of importance to mothers or their babies is available, rather than a simple preponderance of measured 'beneficial' over measured adverse outcomes.

How should this principle be applied to the question of the use of amnioinfusion? Consideration will be given individually to the various indications for amnioinfusion, which fall into three primary categories: antepartum amnioinfusion for oligohydramnios; intrapartum amnioinfusion for potential or suspected umbilical cord compression; and intrapartum amnioinfusion for meconium-stained amniotic fluid.

Antepartum amnioinfusion

Antepartum amnioinfusion has been used firstly to improve ultrasound imaging when there is oligohydramnios (Stringer *et al.* 1990). Apparently there have been no randomized trials to assess the relative risks and benefits of this approach. As the ultrasound procedure is diagnostic and not therapeutic in itself, the clinician would need to have a reasonable expectation of obtaining additional information that would alter management to the benefit of the woman or her fetus, to justify what is clearly an invasive technique.

Antepartum amnioinfusion has also been advocated on the basis of uncontrolled observations in the conservative management of preterm prelabour rupture of the membranes, using an indwelling cervical catheter (Imanaka *et al.* 1989). Until well-controlled evidence of its value is available, the use of this approach should be restricted to further research within randomized trials.

Thirdly, antepartum amnioinfusion has been used in an attempt to prevent the occurrence of fetal lung hypoplasia in pregnancies complicated by oligohydramnios (Fisk *et al.* 1991). Whether the association between oligohydramnios and pulmonary hypoplasia is mediated by reduction of fetal breathing movements is controversial (Fisk *et al.* 1992). As pulmonary hypoplasia is a common cause of perinatal mortality in pregnancies complicated by severe oligohydramnios in the second trimester, the possibility that amnioinfusion may be of benefit is of great clinical importance. Well-controlled randomized trials involving adequate numbers are needed to provide guidance concerning the use of this technique.

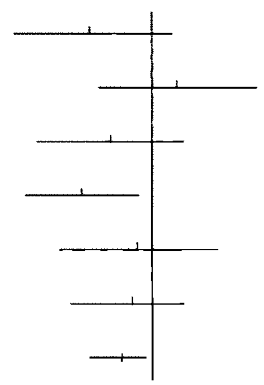
Intrapartum amnioinfusion

Amnioinfusion during labour for potential or suspected umbilical cord compression has been proposed as a rational approach to the prevention or treatment of problems in labour that are associated with oligohydramnios. The indications have included: pre-existing oligohydramnios associated with poor fetal growth or prolonged pregnancy; amniotic fluid loss following prelabour rupture of membranes at or before term; and recurrent variable fetal heart rate (FHR) decelerations presumed to be caused by umbilical cord compression. Warmed normal saline has been infused, using a transcervical catheter, initially at 10–20 ml/minute, either up to a predetermined volume (600–1000 ml) or until an end-point has been reached such as resolution of FHR decelerations (Miyazaki *et al.* 1985) or achievement of an amniotic fluid index of 8 cm (Strong *et al.* 1990) or 10 cm (Macri *et al.* 1991). Thereafter a maintenance infusion at 3 ml/min or intermittent reinfusions have usually been employed.

Several rather small randomized trials of this technique have been reported (Miyazaki & Nevarez 1985; Nageotte *et al.* 1985; Wu *et al.* 1989; Owen *et al.* 1990; Strong *et al.* 1990; MacGregor *et al.* 1991; Nageotte *et al.* 1991; Schrimmer *et al.* 1991), some of which have methodological shortcomings (Hofmeyr 1992a). Meta-analysis of comparable end-points shows reasonable consistency between the trials. Amnioinfusion had no discernable effect on Apgar scores nor umbilical artery pH values, though in one study (Wu *et al.* 1989) 'mild or severe birth asphyxia' was reduced from 36% to 12% (odds ratio 0·23, 95% CI 0·08–0·65). Umbilical cord prolapse occurred in two amnioinfusions and in none of the control group, and perinatal death occurred in two amnioinfusions and in four of the control group, differences which can easily be ascribed to the play of chance. Amnioinfusion was associated with a reduction in the occurrence of variable FHR decelerations (typical odds ratio for two trials 0·20, 95% CI 0·10–0·39), and the frequency of caesarean section (Table 1).

The evidence that amnioinfusion in these circumstances benefits the fetus is limited, but the maternal benefit appears to

Table 1. Meta-analysis of the results of randomized trials reporting the effect of amnioinfusion during labour for potential or suspected umbilical cord compression on caesarean section rate

Study	Treated		Control		Odds ratio (95% CI)	Graph of odds ratio and 95% CI
	n	(%)	*n*	(%)		0·1 0·5 1 2 10
Nageotte *et al.* (1985)	2/29	(6·90)	7/32	(21·88)	0·31 (0.08–1·26)	
MacGregor *et al* (1991)	10/19	(52·63)	7/16	(43·75)	1·41 (0.38–5·24)	
Nageotte *et al.* (1991)	7/50	(14·00)	7/26	(26·92)	0·43 (0.13–1·44)	
Wu (1989)	4/60	(6·67)	14/58	(24·14)	0·26 (0.10–0·71)	
Strong *et al* (1990)	4/30	(13·33)	6/30	(20·00)	0·62 (0.16–2·40)	
Owen *et al* (1990)	8/43	(18·60)	17/57	(29·82)	0·55 (0.22–1·37)	
Typical odds ratio					0·48 (0·30–0·77)	

have been considerable, with an overall halving of the caesarean section rate. The reduction in caesarean sections was accounted for by a reduction in abdominal deliveries for fetal distress. As no mention is made in the reports of the use of fetal scalp blood gas determination to confirm the diagnosis of fetal distress, this diagnosis may have been based on FHR criteria alone and, therefore, overestimated. Amnioinfusion during labour for potential or suspected umbilical cord compression appears to be of proven maternal benefit in situations in which caesarean sections are commonly performed because of abnormal FHR patterns alone. The effect of amnioinfusion where fetal distress is diagnosed by scalp blood sampling remains to be determined.

Intrapartum amnioinfusion for meconium-stained amniotic fluid

A further objective of amnioinfusion is to dilute 'thick' meconium-staining of the amniotic fluid. As thick meconium-staining usually implies a reduction in amniotic fluid volume, the effectiveness of the procedure may also be related to replenishment of amniotic fluid volume. The results of four small randomized trials (Sadovsky *et al.* 1989; Adam *et al.* 1989; Wenstrom & Parsons 1989; Macri *et al.* 1991), again, with certain methodological shortcomings, have been examined in a meta-analysis (Hofmeyr 1992b). Caesarean sections for fetal distress were reduced (typical odds ratio 0·21, 95% CI 0·11–0·41). Overall caesarean section rates were recorded in only two of the reports (typical odds ratio 0·50, 95% CI 0·23–1·10). Measures of neonatal wellbeing at birth tended to favour the amnioinfusion group, in which meconium was less often noted below the vocal cords (typical odds ratio 0·17, 95% CI 0·10–0·29) and meconium aspiration syndrome occurred less frequently (0·18, 0·06–0·54). No perinatal deaths were reported in the amnioinfusion or the control groups. The reservations concerning caesarean sections for fetal distress diagnosed by FHR monitoring, referred to above, apply to these studies as well.

Complications of intrapartum amnioinfusion

While no clinically significant adverse effects were recorded in the randomized trials summarized above, reports of complications associated with intrapartum amnioinfusion include uterine hypertonus (Posner *et al.* 1990) and, though causality was not established, neonatal respiratory failure (Dragich *et al.* 1991). Some scepticism regarding the effectiveness of intrapartum amnioinfusion has been reported (Goodlin 1989, 1991).

Conclusions

A balance needs to be achieved between premature enthusiasm for an exciting new procedure, and therapeutic nihilism. In situations in which caesarean section is commonly performed on the basis of FHR abnormalities alone, the likelihood of reducing operative deliveries would seem to justify the routine use of amnioinfusion in labours complicated by potential or suspected umbilical cord compression. With respect to other indications for amnioinfusion, further randomized trials are urgently needed to confirm or refute the possible important benefits suggested by the studies reported to date.

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British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 452–454

OBSTETRICS

Is obstetric and neonatal outcome worse in fetuses who fail to reach their own growth potential?

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ABSTRACT

Objectives To determine the perinatal outcome of fetuses who had birthweights less than that expected from early third trimester ultrasound scanning.

Design Retrospective estimation of centile fetal weight at early third trimester ultrasound scanning compared with actual centile birthweight corrected for gestational age, parity and sex.

Setting Teaching Hospital Obstetric Unit, London.

Subjects 197 unselected women with singleton cephalic pregnancies who were delivered at term in our unit between October 1989 and May 1990.

Main outcome measures CTG abnormality, need for fetal blood sampling in labour, meconium-staining of the amniotic fluid, mode of delivery, Apgar scores at 1 and 5 min, need for transfer of baby to neonatal unit, and need for neonatal intubation of the neonate at delivery.

Results An actual birthweight >5% less than the birthweight estimated from ultrasound scanning identified 44 babies (22%) with an increased risk of CTG abnormalities ($\chi^2 = 8{\cdot}38, P < 0{\cdot}0025$; Odds ratio (OR) = 2·54; 95% CI 1·36 to 4·78) and need for operative delivery ($\chi^2 = 5{\cdot}81$, $P < 0{\cdot}0125$; OR = 1·94; 95% CI 1·15 to 3·27), when compared with the remainder of the sample. Overall 14 (32%) of this group had birthweights above the 50th centile. A group of 44 babies selected as being the smallest for gestational age, without reference to growth pattern, had a similar excess morbidity. (All this group had birthweights below the 39th centile.)

Conclusions This study supports the hypothesis that *in-utero* fetal growth pattern is as important for perinatal outcome as being small for gestational age *per se*.

Most current definitions of intrauterine growth retardation (IUGR) involve a categorization of birthweight for gestational age. Thus babies <10th centile birthweight for gestational age, are commonly referred to as 'growth retarded'. However 'small-for-gestational age' (SGA) is a better term for this type of categorization as it is likely that many babies <10th centile are small but normal (Goodlin 1990).

It has been suggested that the term IUGR should be reserved for those fetuses that do not reach their full growth potential, even if they are above the 10th centile for weight at birth. It has been further suggested that babies of normal weight who were genetically programmed to be larger but have experienced growth restraint because of *in-utero* factors, are more at risk than the SGA infant per se (Altman & Hytten 1989; Campbell 1989; Pearce & Campbell 1985; Daikoku *et al.* 1979; Hull *et al.* 1978). However, apart from anecdotal case reports (Bradley *et al.* 1988), we could find no record of attempts to analyse perinatal morbidity by growth pattern, rather than by centile birthweight. We therefore carried out a retrospective survey to test the hypothesis that perinatal performance was related to growth potential as determined by an early third trimester ultrasound scan.

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Subjects and methods

We studied 197 unselected women with a singleton pregnancy and a cephalic presentation at delivery, who had a routine early third trimester ultrasound scan (between 28 and 34 weeks gestation as part of an existing policy to detect intrauterine growth retardation), and who were delivered at term at our hospital between October 1989 and May 1990. All women had an ultrasound scan at 18–20 weeks gestation to confirm dates and to screen for major structural anomalies. (All scans were performed at a hospital antenatal clinic on a Siemens SL2 machine) Measurements of fetal biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) were made at the early third trimester scan. From these measurements a fetal weight was estimated (Hadlock *et al.* 1985) and the standard deviation and centile weight for the gestational age at the time of the scan obtained from published data (Jeanty *et al* 1984). An estimate of birthweight was then calculated (to the nearest 50 g) by assuming no change in centile between scan and birth and then using the nomogram described by Altman & Coles (1980), corrected for gestational age, sex and parity. Actual birthweight (ABW) and estimated birthweight (EBW) were then compared, and the percentage change between the actual and the estimated birth-

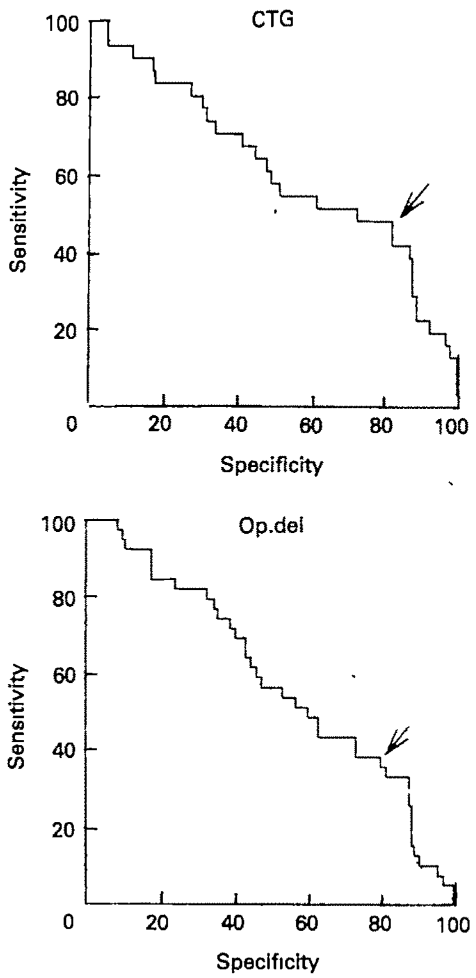

Fig. 1. Receiver operator curves for cardiotocograph (CTG) abnormality and need for operative delivery using percentage change between estimated birthweight and actual birthweight as screening test. (For explanation of arrow, see text)

weights was calculated. (Percentage change = (ABW-EBW)/EBW x 100).

The presence of an abnormal cardiotocograph pattern (CTG) in labour, meconium staining of the amniotic fluid, intrapartum fetal blood sampling and pH (when taken), the mode of delivery, Apgar scores at 1 and 5 min, the need for neonatal intubation and admission to the neonatal intensive care unit (NICU) were noted. This information was obtained from the St Mary's Maternity Information System.

Discriminant analysis was performed using commercially available statistical software (SPSS PC+; SPSS Inc., Chicago, USA), comparing the percentage change as calculated above, and the centile birthweight corrected for sex, parity and gestational age. Receiver-operator curves were constructed for percentage change for each outcome parameter.

Results

The actual birthweight (ABW) was greater than the estimated birthweight (EBW) in 113 babies (57%), and was lower in 85 (43%), (*P* >0·05; ns). The mean ABW was 3384 g (SD 487 g) and the mean EBW was 3308 g (SD 332 g), (*t* = 1·83; ns). There were only 10 babies (5%) born with birthweights below the 10th centile as defined by Altman & Coles (1980). There were no perinatal or neonatal deaths in this series and none of the babies had hypoxic-ischaemic encephalopathy (HIE).

Discriminant analysis showed that percentage change between ABW and EBW was significantly related to CTG abnormality (*P* = 0·02), and need for operative delivery (*P* = 0·05). Centile birthweight was significantly related to abnormal CTG (*P* = 0·01) only. No other significant correlations were found using discriminant analysis.

Using receiver-operator curves (Fig. 1), in which sensitivity was plotted against specificity for all 196 possible cut-offs of percentage change, showed that a drop of more than 5% from the EBW to ABW (arrowed in figure) gave a sensitivity of 48% and specificity of 82% for CTG abnormality, and a sensitivity of 36% and specificity of 80% for operative delivery. This cut-off selected 44 babies (22%), and in this group there was significantly more CTG abnormality (χ^2 = 8·38, *P* <0·0025; odds ratio (OR) = 2·54; 95% CI 1·36 to 4·78), and need for operative delivery (χ^2 = 5·81, *P* <0·0125; OR = 1·94; 95% CI 1·15 to 3·27) than in the rest of the sample. When the 44 babies with the lowest birthweight for gestational age were studied, they were all below the 39th centile as defined by Altman & Coles (1980). They also had significantly more abnormal CTGs (χ^2 = 6·83, *P* <0·005; OR = 2·36; 95% CI 1·25 to 4·7) than the rest of the sample but were not more likely to need operative delivery. When the two groups were compared, there was a significant difference between their mean centile birthweights (*t* = 3·57; *P* <0·001). (see Fig. 2). Overall 14 babies (32%) in the group with a >5% fall had actual birthweights above the 50th centile (25 babies fell into both groups).

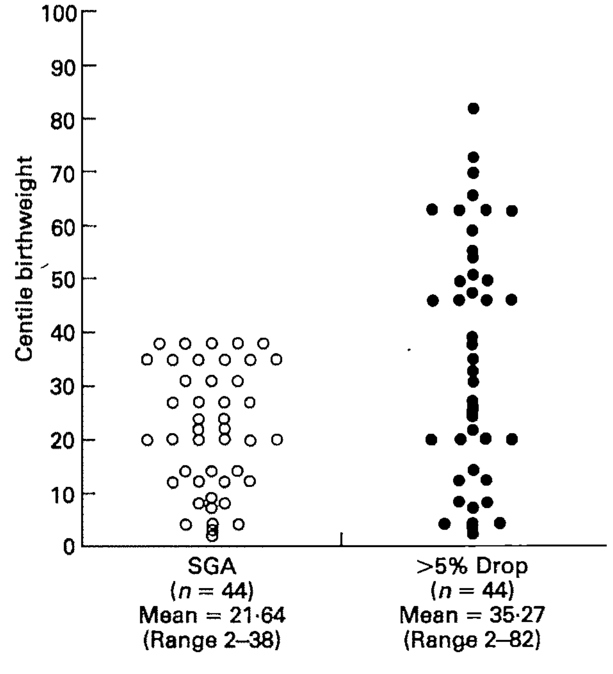

Fig. 2. Comparision of centile birthweights (*t* = 3·57; *P* <0·001). Small-for gestational age (SGA) = lowest 22% of sample by centile birthweight. >5% Drop = babies with actual birthweight >5% less than estimated birthweight.

Discussion

The results of this study support the hypothesis that growth pattern is as closely related to perinatal performance as actual size at delivery. There were significant increases in CTG abnormalities and operative delivery in the 22% of our population with a >5% fall in centile weight during the third trimester, even though 32% of them were above the 50th centile (weight for gestational age) at birth. This latter group of babies would not normally be categorized as 'at risk' by most current clinical criteria. Those babies who have a fall in growth rate as defined here have the same intrapartum and neonatal morbidity as those which are SGA.

We now need to examine the hypothesis that the fall in growth rate can be detected antenatally by ultrasound, as opposed to determined after birth. We are currently conducting a prospective trial to test this hypothesis. Two third trimester ultrasound scans will be performed in an attempt to diagnose any fall in growth rate and to ascertain whether an ultrasound detected fall will be predictive of the abnormal outcomes identified in this retrospective study. Doppler studies will also be performed at the time of the second scan. Even if a fall in growth rate can be measured reliably, any benefit in outcome will depend upon effective management strategies. Whether such strategies are available is at present open to question. This issue will be examined by a subsequent trial in which 50% of the scan results are revealed and 50% concealed.

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Received 7 February 1991
Resubmitted 24 June 1991
Accepted 2 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol 99, pp. 455–458

OBSTETRICS

Sweeping of the membranes is an effective method of induction of labour in prolonged pregnancy: a report of a randomized trial

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ABSTRACT

Objective To determine whether sweeping of the membranes is an effective method of induction of labour in women with prolonged pregnancy.
Design Randomized controlled trial.
Setting: A district maternity hospital.
Subjects 65 women attending an antenatal clinic; 33 randomized to sweeping of the membranes and 32 to a control group.
Main outcome measure Proportion of women achieving spontaneous labour.
Results Spontaneous labour occurred more often in the sweeping of the membranes group than in the control group (25/33 (76%) *vs* 12/32 (38%); odds ratio (OR) 4·65; 95% confidence interval (CI) 1·75 to 12·31; *P* = 0·002). In addition a greater proportion of women in the sweeping group had a cervical dilatation of 4 cm or more at the first vaginal examination in the labour ward (16/33 (49%) *vs* 5/32 (16%); OR 4·39; 95% CI 1·56 to 12·32; *P* = 0·005). There were fewer maternal infections in the sweeping group (0/33 *vs* 4/32 (12%); OR 0·12; 95% CI 0·02 to 0·88; *P* = 0·04). There were no differences in the type of analgesia used in labour, the mode of delivery or neonatal outcome.
Conclusions Sweeping of the membrances is an effective method of induction of labour in women with prolonged pregnancy.

Formal induction of labour in women who are 'past dates' is still a common obstetric procedure, despite doubts about its usefulness (Gibb *et al.* 1982; Cardozo *et al* 1986; Yudkin & Redman 1986; Augensen *et al.* 1987). Yet the methods of induction of labour which are commonly used have complications some of which are serious. Thus amniotomy can result in intrauterine infection, fetal heart rate decelerations, umbilical cord prolapse, and bleeding from fetal vessels in the membranes, from the placenta or from the cervix. Oxytocin and prostaglandin administration can result in excessive uterine contractions, which may lead to fetal hypoxia, precipitate labour, postpartum haemorrhage, tentorial tears in the newborn, and uterine rupture (Geirsson 1981; Scott & Richter 1981; Budden 1982; Stronge *et al.* 1987). Intravenous oxytocin infusions have fewer problems than vaginal prostaglandin pessaries or gel, since the uterine hyperstimulation of an oxytocin infusion is more easily controlled than that of a depot prostaglandin; yet vaginal prostaglandins are a very common method of induction of labour. These complications, though rare, are serious enough to result in the welcoming of any strategy that will reduce the need for these methods of induction labour.

Sweeping of the membranes at term has been used for 180 years as a method of induction of labour, yet there have been few controlled comparisons of its effectiveness.

Theoretically sweeping of the membranes should have a powerful effect in stimulating labour, since the procedure causes an increase in prostaglandin metabolites in the maternal circulation (Mitchell *et al.* 1977). Furthermore the extent of this prostaglandin release is proportional to the area of membranes separated from the uterus (Keirse 1983). However, there have been only three attempts to assess formally the effectiveness of sweeping of the membranes as a method of induction of labour (Swann 1958; Weissberg & Spellacy 1977; McColgin *et al.* 1990). Swann's study was a quasi-randomized trial and showed that sweeping of the membranes resulted in spontaneous labour more often than in the control group (69% *vs* 26%). In view of the selection biases in that study the conclusion that sweeping of the membranes resulted in such a big difference in the two groups must be in doubt. The trial by Weissberg & Spellacy (1977) also had selection biases: in the group allocated to sweeping there were more primigravidae, and more women had a Bishop's score >6. In the trial by McColgin *et al.* (1990) the method of randomization was not described and there was no table of patient characteristics, and so it was impossible to judge whether there was any bias in the allocation of women to the two groups.

It was the uncertainty of the place of sweeping of the mem-

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Table 1. Characteristics of the subjects in the two groups.

Variable	Sweeping ($n = 33$)	Control ($n = 32$)
Age (years)	27·2 (4·7)	25·3 (5·1)
Gestational age (days)		
At recruitment	286·6 (2·8)	286·3 (2·8)
At planned induction	290·4 (2·6)	289·8 (1·9)
Interval between recruitment & induction (days)	4·0 (1·0)	3·8 (1·5)
Parity		
Primigravidae	17	14
Multigravidae	16	18
Birthweight (kg)	3·67 (0·35)	3·67 (0·43)

Results are mean (SD) values.

branes in the induction of labour that made us undertake this randomized trial.

Subjects and methods

The trial was confined to one antenatal clinic responsible for about 700 women each year, and lasted from June 1990 to March 1991. It was the policy at that antenatal clinic to offer induction of labour between 41 and 42 weeks gestation; those women who preferred not to undergo induction had a twice-weekly ultrasound biophysical profile performed. Women who opted for induction of labour were randomly allocated to undergo sweeping of the membranes or to act as controls. Sweeping of the membranes was performed by one of the authors (M. E.-T.). Clean examination gloves were used, lubricated with jelly (Lubricating Jelly, Pearce Laboratories, Leeds) or obstetric cream (1% w/w chlorhexidine gluconate); as much of the membranes as possible was separated from the lower segment. If the cervix would not admit a finger it was massaged vigorously to encourage prostaglandin release. No subject experienced discomfort from the sweeping or massaging other than that associated with a vaginal examination. Women allocated to act as controls did not have any form of vaginal examination. After allocation the subjects were given a date for formal induction of labour.

The radomization process was by random permuted blocks, the randomization codes being placed in opaque sealed envelopes which were kept in the antenatal clinic. The main endpoint of the trial was the proportion of women in each group who went into spontaneous labour (and therefore did not require induction by more elaborate methods). Based on the study by Swann (1958), where 26% of the controls achieved spontaneous labour while awaiting induction, in order to demonstrate a doubling of this proportion with sweeping, 110 subjects would have to be randomized ($\alpha = 0{\cdot}05$; $1-\beta = 0{\cdot}80$).

Spontaneous labour was defined as self-admission of the subject to the hospital with painful regular contractions occurring twice in 10 min or more often. A cervical dilatation of 4 cm or more on entry to the labour ward was considered arbitrarily to indicate the active phase of labour in women who were admitted in labour, or imminent active phase in those admitted for formal induction of labour.

Maternal pyrexia in labour or the puerperium was defined as an axillary temperature of 37·1°C or above on at least two occasions.

Since the trial was of a procedure in common use in the practice of the hospital with no apparent serious side-effects, formal ethical approval of the study was not sought. The women randomized to the control group were not aware that they were taking part in a randomized trial. Those who were randomized to sweeping were informed of the purpose of the trial and the procedure of sweeping of the membranes. None of the women allocated to sweeping refused to participate in the trial. All the women were recruited at the antenatal clinic.

Continuous variables in Table 1 were described by the mean and standard deviation. Categorical outcomes in the two groups were compared by odds ratios (OR) and 95% confidence intervals (CI).

Table 2 Sweeping of the membranes trial—outcomes

	Sweeping	Control	Odds ratio	(95% CI)	P
Labour					
Spontaneous labour	25 (76%)	12 (38%)	4·65	(1·75, 12·31)	0·002
Cervix >4 cm at first exam	16 (49%)	5 (16%)	4·39	(1·56, 12·32)	0·005
Maternal infection					
Pyrexia	0	4 (12%)	0·12	(0·02, 0·88)	0·04
Antibiotics	0	4 (12%)	0·12	(0·02, 0·88)	0·04
Analgesia in labour					
Gas & air only	6 (18%)	3 (9%)	2·07	(0·51, 8·36)	0·30
Pethidine	14 (42%)	11 (34%)	1·40	(0·52, 3·77)	0·50
Epidural	13 (39%)	18 (56%)	0·51	(0·20, 1·35)	0·17
Mode of delivery					
Caesarean section	5 (15%)	4 (12%)	1·24	(0·31, 5·03)	0·76
Forceps	2 (6%)	3 (9%)	0·63	(0·10, 3·86)	0·62
Spontaneous	26 (79%)	25 (78%)	1·04	(0·32, 3·36)	0·95
Neonatal outcomes					
Apgar score <6					
1 min	2 (6%)	6 (19%)	0·31	(0·07, 1·37)	0·12
5 min	1 (3%)	1 (3·1%)	0·97	(0·06, 15·84)	0·98
Serious infection	0	0			
Perinatal death	0	0			

Results

Thirty-three women were randomized to sweeping and 32 to act as controls. It was possible to perform sweeping of the membranes in 27 women, whereas in six women in the sweeping group massaging of the cervix was undertaken because of an unfavourable cervix. The characteristics of the women are shown in Table 1. The groups were well matched for age, gestational age at recruitment and at planned induction of labour, parity and birthweight. Table 2 shows the outcome of the trial.

More women randomized to sweeping went into spontaneous labour than in the control group (25/33 (76%) *vs* 12/32 (37%); OR 4·65; 95% CI 1·75 to 12·31; $P = 0{\cdot}002$). Because of this marked difference in the proportions of subjects achieving spontaneous labour the trial was stopped before 110 women were recruited. The decision to stop the trial was made by the authors themselves, the decision being based on the statistical stopping rule for randomized trials (Pocock, 1983). Twenty-four out of the 27 women (89%) in the sweeping group who underwent sweeping of the membranes went into labour spontaneously, compared with 1 of the six (17%) who had cervical massage. Of the 25 women in the sweeping group who achieved spontaneous labour 11 (44%) went into labour within 24 h of the sweeping, 18 (72%) within 48 h and 21 (84%) within 72 h.

All the women who had a cervical dilatation of 4 cm or more on entry to the labour ward were in labour. More women randomized to sweeping had a cervical dilatation of 4 cm or more than in the control group (16/33 (48%) *vs* 5/32 (16%); OR 4·39; 95% CI 1·56 to 12·32; $P = 0{\cdot}005$).

Fewer women randomized to sweeping of the membranes had a pyrexia in labour or the puerperium and required antibiotics (0/33 *vs* 4/32 (12%); OR 0·12; 95% CI 0·02 to 0·88; $P = 0{\cdot}04$). The type of analgesia in labour, mode of delivery and neonatal outcome were similar in the two groups.

Discussion

This trial shows that sweeping of the membranes is an effective method of induction of labour in women in the 42nd week of gestation: three-quarters of the women in the sweeping group went into labour spontaneously compared with just over one-third of the control group. In any obstetric service the rate of induction of labour for prolonged pregnancy varies greatly, being largely determined by the views of the obstetrician responsible for the service and the views of the pregnant women who are past their dates. This study shows that no matter what the induction rate for past dates, sweeping of the membranes will result in a substantial reduction in the number requiring induction by a more elaborate clinical procedure. Thus if a particular antenatal clinic has an induction rate of 20% then from the estimate of the odds ratio in this trial the need for the use of an oxytocic agent or rupture of the membranes for induction will be reduced to 5%, with a 95% CI of 2% to 12%. If, however, an antenatal clinic adopts a more conservative approach to induction of labour for prolonged pregnancy and has an induction rate of 5%, then from the estimate of the odds ratio in this trial the use of oxytocics or rupture of the membranes would be reduced to 1%, with a 95% CI of 0 to 3%—still a substantial reduction.

Not only did more women in the sweeping group achieve spontaneous labour, substantially more were admitted to the labour ward in the active phase of labour: nearly half were admitted in the active phase in the sweeping group compared to one-sixth of the controls (Table 2).

One of the worries of sweeping of the membranes is the possible introduction of infection into the extra-amniotic space that could cause chorio-amnionitis, and it was the increase in maternal infections with sweeping that led Swann (1958) to abandon the procedure. In our trial four women developed pyrexia in labour of the puerperium, all of whom received antibiotics for actual or supposed infection and all these women were in the control group. Although the trial estimate of the odds ratio of 0·12 with sweeping of the membranes is substantial, and is significant statistically at the conventional 5% level, the 95% CI interval of this odds ratio is wide, implying that the study is too small to make any definitive statements on any resulting risk of chorio-amnionitis.

There is some suggestion that induced labours are more painful than spontaneous labours and it might be thought that there would be more need for epidural analgesia in the control group. Rate of epidural analgesia was not a main end-point in the trial, and although there were more epidurals in the control group, this difference could have arisen by chance. Similarly, the trial was too small to be able to show any differences in the mode of delivery or neonatal outcome.

There is still the problem of the unripe cervix in women requiring induction of labour. In prolonged pregnancy probably the safest course is to carry out frequent biophysical profile scores until spontaneous labour supervenes or until the cervix becomes favourable. In some situations induction of labour will be essential even with an unfavourable cervix. Vaginal prostaglandins are commonly used, but even with an unripe cervix, hyperstimulation of the uterus can occur (Stronge *et al.* 1987). One alternative is to perform hydrostatic sweeping of the membranes through an extra-amniotic Foley catheter. A trial of this method is now under way.

In conclusion, this trial shows that sweeping of the membranes in women with prolonged pregnancy is an effective method of inducing labour, without apparent harm to mother or baby.

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Received 20 May 1991
Accepted 9 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 459–463

OBSTETRICS

An economic evaluation of daycare in the management of hypertension in pregnancy

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ABSTRACT

Objective To evaluate the efficiency of daycare in the management of hypertension in pregnancy compared with inpatient management with prior domiciliary visits.
Design Comparative study.
Setting Two maternity teaching hospitals, Glasgow Royal Maternity Hospital which has an established daycare unit and Aberdeen Maternity Hospital with no daycare unit.
Main outcome measures Pregnancy outcomes in terms of maternal hypertensive complications, gestation at delivery, mode of delivery, birthweight, Apgar scores, admission rates and length of admission to special care baby unit.
Results There was no significant difference in any of the measured pregnancy outcomes between the two hospitals. The average cost of treating a woman with mild hypertension was £154·91 in Glasgow and £136·59 in Aberdeen. The average cost of treating women with a single episode of hypertension and women with a past history of hypertension was £88·65 and £214·12 in Glasgow and £31·18 and £28·28 in Aberdeen, respectively. If these two groups are excluded, the average cost of treating women with mild hypertension was £172·32 in Glasgow and £201·13 in Aberdeen. The majority of women were willing to attend daycare five times per week to avoid admission.
Conclusion Daycare management of hypertension in pregnancy is more efficient than inpatient care with prior domiciliary visits for most women, but less efficient for women with transient or previous hypertension. It is very acceptable to women. Domiciliary checking of women with hypertension found at outpatient clinics would reduce resource use.

In 1988 data from the standard statistical document for all discharges from Scottish maternity hospitals showed that 13% of all pregnancies were complicated by hypertension. Other studies have suggested that the true incidence is higher; Redman (1982) estimated that 25% of pregnant women will have a diastolic measurement of ≥90 mmHg.

Traditionally women with hypertension in pregnancy are admitted to hospital for rest, assessment and treatment. The introduction of a daycare service has been seen as a means of reducing inpatient workload and costs. These effects were observed following the introduction of daycare for cancer care and surgery (Mor *et al.* 1988; Prescott *et al.* 1978). Daycare has been growing in use since 1981 in Scotland; a survey in 1989 showed that 12 out of 22 maternity units had a designated daycare area (Rosenberg & Twaddle 1990).

While daycare is becoming more widespread in the management of hypertension in pregnancy, there has been no formal assessment of the economic and social effects of its use on the health service and on the women involved. This paper describes such a study which aimed to assess these effects in two teaching hospitals with similar numbers of deliveries. The study hospital was Glasgow Royal Maternity Hospital which has had a daycare facility since 1981, and the control hospital was Aberdeen Maternity Hospital where the majority of care for hypertension is carried out on an inpatient basis but where some women receive domiciliary midwife visits to check blood pressure.

The rationale for the study was the belief that as the incidence and outcomes of hypertensive pregnancies were similar in the two hospitals the different modes of management for mild hypertension could be studied. Management of severe hypertension and pre-eclampsia was assumed to be the same at both hospitals with women receiving inpatient care. The difference between the two units in terms of cost and satisfaction to women could then be compared.

Subjects and methods

The economic evaluation took the form of a cost minimization analysis, which is used when two alternatives have outcomes that are achieved to the same extent and thus 'the efficiency

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evaluation is essentially a search for the least cost alternative' (Drummond *et al.* 1987). Under cost-minimization analysis average cost per woman in each group is calculated and the preferred option is the one which offers the lowest cost. However, within the mild hypertensive group attention would be given to particular categories, such as transient hypertension and past history of hypertension.

A total of 100 consecutive attenders with hypertension was recruited from the daycare unit in Glasgow and 100 consecutive inpatients in both centres. In addition, women who were seen by the domiciliary midwife service in Aberdeen during the time taken to recruit the 100 inpatients were also included. Further details about sample size and recruitment have been given elsewhere (Rosenberg & Twaddle 1990).

Data were collected for the main study from the case records of each woman. These related to basic demographic information, obstetric and medical history, history of hypertension in the current pregnancy, all hypertensive-related resource use and maternal and fetal outcome.

Actual costs for each element of hypertension-related care, such as inpatient days, daycare attendances, tests and so on, were calculated so that individual patient costs could be compared, using the method of Russell (1974). However, following the approach used by Harper (1975), a single set of unit costs was calculated, so that any differences in costs were a result of different resource use and not different hospital operating characteristics. The costs used were an estimate of the average variable cost, including tests, medical and nursing input, and hotel type care, and were estimated from the 'care plans' of the departments concerned. Details of the cost calculations are given in Appendix 1.

Women's views were elicited by means of a structured interview to determine how they felt about the care they had received and also their preferences for daycare or inpatient care. Information about costs to women of the various types of care, in terms of loss of earnings and 'out of pocket expenses' was collected by questionnaire. Information about disruption to normal activity was also collected so that a valuation of time foregone for other activities could be included. A different value for lost leisure time and lost work time, including housework, is imputed (Department of Transport 1987).

Women were categorized into one of three groups corresponding to their experience of hypertension throughout their entire pregnancy. By adopting this approach, 'like with like' comparisons could be made between the two centres. Groups were defined as: group A, mild hypertension, with diastolic blood pressure 90–99 mmHg inclusive and no significant proteinuria; group C, severe hypertension with diastolic blood pressure consistently >99 mmHg or significant proteinuria; and group B, mixed hypertension where the woman had experienced periods of both mild and severe hypertension. Since the study question addressed here relates to daycare as an option in the management of mild hypertension, the groups which will be considered in this paper are groups A and B. Group A was further subdivided into a group with transient hypertension (diastolic blood pressure of ≥90 mmHg once only) and a group with sustained hypertension. Women with chronic or previous hypertension were identified separately.

To test the comparability of the two centres in terms of incidence of hypertension, a separate study was conducted. This involved analysis of case notes of all women who were delivered in four separate 7-day periods during 1989.

The results of comparisons between the two centres were analysed using the Statistical Package for the Social Sciences (SPSSPC) and the Confidence Interval Analysis package (CIA). Statistical significance was measured by *t*-tests for means, χ^2-test for categorical data and the two sample Kolmogorov-Smirnov test for comparison of distributions.

Significance levels of $P \leqslant 0.05$ are reported as significant.

Results

Incidence of hypertension

Case notes of 378 women in Aberdeen and 320 women in Glasgow who were delivered during the four 7-day study periods were analysed. Using a working definition of hypertension as a diastolic blood pressure reading of ≥90 mmHg, the incidence of hypertension was found to be 13·5/100 deliveries in Aberdeen and 17·5/100 in Glasgow. The difference was not significant ($\chi^2 = 0{\cdot}24$, df = 1, $P = 0{\cdot}62$). This supports the assumption that the two centres are comparable.

Group characteristics

Table 1 shows a comparison of basic information for women with mild hypertension (group A) and a mix of mild and severe hypertension (group B). This is to ensure that 'like-with-like' comparisons are being made. In neither group were the characteristics of the women significantly different: for group A mean age ($t = -1{\cdot}21$, $P = 0{\cdot}23$), parity ($\chi^2 = 0{\cdot}3$, df = 1, $P = 0{\cdot}58$), previous history of hypertension ($\chi^2 = 0$, $P = 1$) and transient hypertension ($\chi^2 = 1{\cdot}14$, df = 1, $P = 0{\cdot}71$) and group B mean age ($t = 0{\cdot}86$, $P = 0{\cdot}39$), parity ($\chi^2 = 0{\cdot}15$, df = 1, $P = 0{\cdot}69$) and previous history of hypertension ($\chi^2 = 0{\cdot}05$, df = 1, $P = 0{\cdot}83$).

Group outcomes

Table 2 shows the outcomes for singleton pregnancies only.

Table 1. Characteristics of the women in the study groups

	Group A*		Group B†	
	Glasgow ($n = 62$)	Aberdeen ($n = 34$)	Glasgow ($n = 66$)	Aberdeen ($n = 56$)
Maternal age (years)				
Mean (SD)	27 (5·1)	28 (5·2)	28 (6·2)	27 (4·9)
Parity				
Nulliparous	31	19	45	40
Parous	31	15	21	16
Multiple pregnancies	1	0	2	0
Previous hypertension	14	7	14	11
Transient hypertension	22	10	–	–

*Group A includes women with mild hypertension (diastolic blood pressure 90–99 mmHg and no significant proteinuria).

†Group B includes women who had experienced periods of both mild and severe hypertension (diastolic blood pressure >99 mmHg or significant proteinuria).

Table 2. Details of outcome in the study groups

	Group A		Group B	
	Glasgow ($n = 61$)	Aberdeen ($n = 34$)	Glasgow ($n = 64$)	Aberdeen ($n = 56$)
Median gestation at delivery (weeks)	40	40	38	39
Preterm deliveries (<37 weeks)	1	0	12	10
Mode of delivery				
Spontaneous vaginal	39	22	29	30
Caesarean section	13	5	25	14
Forceps	9	7	10	12
Birthweight (kg) mean (SD)	3.5 (0·5)	3.4 (0·5)	3·04 (0·9)	3·05 (0·7)
5-min Apgar score <7	3	0	4	1
Admissions to SCBU	3	2	14	9

SCBU = special care baby unit.
For explanation of groups A and B see Table 1.

There were no significant differences for any factor between the two hospitals in either of the two groups: for group A mean birthweight ($t = 0·95$, $P = 0·34$), mode of delivery ($\chi^2 = 0·95$, df = 2, $P = 0·62$), and distribution of gestation at delivery (K-S Max = 0·25, K-S Z = 1·9, $P = 0·11$), and for group B mean birthweight ($t = 0·02$, $P = 0·98$), mode of delivery ($\chi^2 = 2·78$, df = 2, $P = 0·25$), and distribution of gestation at delivery (K-S Max = 0·11, K-S Z = 0·61, $P = 0·85$)).

Since characteristics and outcomes were similar and the distribution of gestation at delivery was not significantly different, cost minimization analysis is the correct form of economic analysis to use in the study.

Antenatal resource use

Table 3 details the number of women admitted in each group and the average number of inpatient days, domiciliary visits and daycare attendances for women who received these elements of care. For women admitted in the two centres there was no significant difference in length of stay: group A ($t = 0·15$, $P = 0·88$), group B ($t = -1·24$, $P = 0·22$). The odds of being admitted in Aberdeen in each group are very much higher than in Glasgow: group A (odds ratio = 6·53, 95% CI 2·21 to 19·3); group B (odds ratio = 11·0, 95% CI 1·37 to 88·1).

Table 3. Antenatal resource use in the study groups

	Group A		Group B	
	Glasgow ($n = 62$)	Aberdeen ($n = 34$)	Glasgow ($n = 66$)	Aberdeen ($n = 56$)
Admitted *n* (%)	6 (10)	14 (41)	55 (83)	55 (98)
Inpatient days mean (SD)	4·2 (3·4)	4·0 (2·6)	6·7 (6·9)	7·2 (10·1)
No. of visits mean (SD)				
Daycare	2·2 (2·4)	–	3·6 (3·0)	–
Domiciliary midwife	–	2·5 (2·5)	–	5·2 (4·4)

For explanation of groups A and B see Table 1.

Costs to the NHS

Cost comparisons are shown in Table 4. The costs used were £74·27 per inpatient day, £60.06 per daycare attendance and £6·53 per domiciliary midwife visit. There were no significant differences in mean costs per pregnancy between Glasgow and Aberdeen, but there was a significant difference in the distribution of costs in group A (K-S Max = 0·559, K-S Z = 2·619, $P < 0·005$), with 68% of women in Aberdeen having a total cost of less than £100 compared with 55% in Glasgow. The distribution of costs in group B was not significantly different (K-S Max = 0·17, K-S Z = 0·93, $P = 0·35$).

The cost of domiciliary midwife visit has been estimated at £6·53 and the cost of a visit to a daycare at £60·06; thus, the minimum cost implication of an episode of transient hypertension in Glasgow is more than nine times as great as in Aberdeen. The cost of treating a case of transient hypertension was on average £88·65 in Glasgow and £31·18 in Aberdeen, which is significantly different ($t = 2·22$, $P = 0·03$).

Women with a history of hypertension in pregnancy and those with pre-existing hypertension are treated as daycare patients throughout their pregnancies in Glasgow. This allows greater supervision and closer monitoring of the women and reassures both the pregnant woman and the clinicians involved. Several of the women in the study were in this category. However, inclusion of these women on the cost side of the equation ignores benefits such as reassurance, which may be greater than the reassurance received during domiciliary care. The cost of treating a woman with a past history of hypertension in group A was on average £214·12 in Glasgow and £28·28 in Aberdeen ($t = 3·23$, $P = 0·006$).

Therefore, excluding women with either transient or a past history of hypertension gives an average cost of treating women with mild hypertension of £172·32 in Glasgow and £201·13 in Aberdeen. Thus, the Glasgow based system has a lower cost for both group A and group B than the Aberdeen based system. There was, however, no significant difference in cost: group A ($t = -0·51$, $P = 0·61$) and group B ($t = -0·49$, $P = 0·63$)

Costs of the users of the system

Costs to the users of the system include both loss of earnings and 'out of pocket' expenses for childcare and travel to both the women concerned and their families. In addition, there is the value of time foregone for other uses and thus an estimate of this opportunity cost is included. Table 5 shows the costs calculated. The average cost to women in Aberdeen over her whole

Table 4. Cost per woman using comparison costs

	Group A		Group B	
Cost (£)	Glasgow ($n = 62$)	Aberdeen ($n = 34$)	Glasgow ($n = 66$)	Aberdeen ($n = 56$)
Mean	154·91	136·59	609·71	668·48
Range				
Minimum	60·06	0·00	60·06	19·59
Maximum	937·09	594·16	3402·21	3578·81

For explanation of groups A and B see Table 1.

Table 5. Out of pocket expenses to women and opportunity cost of time foregone

Resource use	Average cost to woman & family (£)	Average opportunity cost (£)
One visit		
Daycare	6·73	15·44
Domiciliary midwife	0·50	0·56
One day as inpatient		
Glasgow	4·35	41·63
Aberdeen	3·67	40·12

pregnancy was £17·12 and in Glasgow £39·85. The estimated opportunity costs of time foregone was £246·47 in Aberdeen and £102·99 in Glasgow. These costs were not significantly different ($t = -1{\cdot}91$, $P = 0{\cdot}06$)

Women's views

Thirty women were interviewed during daycare in Glasgow and 18 women were interviewed as inpatients in Aberdeen. In general the women were enthusiastic about the care they had received. Of the daycare attenders, 27 mentioned benefits such as reassurance, monitoring and avoidance of admission; 15 of them also mentioned disadvantages, the length of time spent in daycare being the most common.

Of the 18 women interviewed in Aberdeen, 15 mentioned benefits of being in hospital, the most common were reassurance, rest and monitoring. Two women stated that there were no benefits to being in hospital. Sixteen women mentioned disadvantages, such as hospital food and the length of the day. In addition, eight women had experience of domiciliary midwife blood pressure checks and all these women had an extremely positive view of this service.

In both centres women were asked how many visits to daycare they would be willing to make in one week when the alternative was a 7 day hospital stay. It was explained that the tests carried out under the two settings would be the same. Seventeen women in Glasgow and 11 in Aberdeen were prepared to come to daycare 5 times per week. The main reason given by these women was avoidance of staying in hospital. Those less willing to come to daycare mentioned inconvenience and travel. The one woman in Aberdeen who did not want to come to daycare at all had a poor past obstetric history.

Discussion

The cost of an inpatient day and a daycare attendance were found to be of a similar order of magnitude. This should be expected because one daycare attendance is a substitute for an inpatient stay rather than an inpatient day. That is, one daycare attendance may be considered to be an alternative to a 3-day inpatient stay for example, involving the same number of tests etc, in a shorter time period. The intensity of resource use in the two settings can be illustrated by a comparison of the cost per hour; in daycare this is £12·01 compared with £3·09 for inpatient care. This corresponds to a 4 to 1 ratio of resource use intensity.

The daycare system was found to be significantly more expensive for the following groups with mild hypertension: transient hypertension, pre-existing hypertension and previous hypertension in pregnancy. There was no significant difference in cost for other mild hypertensives. However, the trend suggests that daycare would be cheaper for the latter group.

Both components of costs to women (expenses and opportunity costs) are higher when a trip to hospital is involved rather than a domiciliary visit; this is particularly true when the woman is admitted. Total costs to women are higher in Aberdeen. Although 'out of pocket' costs are higher in Glasgow, the opportunity costs of inpatient admission more than outweigh this. Despite this finding women may feel this cost is justified.

Overall, the views of care received were favourable. In particular, domiciliary midwife visits were very popular, as was daycare, but since many women mentioned monitoring as a benefit of daycare or inpatient care it is not clear if women would prefer this form of care for their whole hypertensive episode or would prefer a mix of the two systems.

One important question in such analyses is whether any potential cost savings identified can be translated into actual savings to the health service. Studies from other forms of daycare (Haworth & Balarajan 1987; Watts & Pearce 1988) have suggested that this is not necessarily the case. For the full cost savings of a daycare system to be realized requires the satisfaction of several conditions. Beds freed must be closed and not redeployed for other uses; there should be no set up or conversion costs; and there should be no change in the threshold for care.

Transition to daycare may be costly, involving conversion or capital investment; however, the results of this study show that revenue savings could result from its introduction. The decision to invest in daycare will depend partially on the 'pay-back' period for the investment. Further analysis of these factors is necessary and will be addressed elsewhere (Twaddle & Harper, in preparation).

The study has shown that there is a lower cost per pregnancy for certain groups of women managed under a daycare system, although the differences in cost were not significant. The daycare system is significantly more expensive for some groups of women, including transient hypertensives, which suggests that a system which screens out those with transient hypertension before proceeding to the more expensive daycare system may offer a cost effective solution. This screening device could be domiciliary midwife visits, which were found to be very popular with the women interviewed, general practitioner checks or additional clinic visits.

Acknowledgments

This research was supported by the Chief Scientists's Organization, Scottish Home and Health Department. We thank Drs M. Hall, G. McIlwaine, Mrs B. MacLennan, Drs K. Rosenberg and J.J. Walker for supervising this research. We also thank the staff of Glasgow Royal Maternity Hospital and Aberdeen Maternity Hospital for their assistance, Sister Helen Cheyne for her help in data collection, Colin Pritchard for statistical assistance and Andrew Walker for comments on earlier drafts of this paper.

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Appendix 1

Cost calculations for different systems of care

Costs used in the comparison are estimated for daycare and inpatient care in Glasgow. Using care plans for hypertensive patients in the two settings, costs are estimated for medical and nursing input, tests and hotel type care including catering, heat, light etc. All costs are expressed in 1989 prices.

Domiciliary midwife blood pressure (BP) checks are estimated from Aberdeen, using observational data. Costs for these checks include nursing input, travelling for the midwives and a share of the costs associated with the midwives' base. An average visit takes 30 mins including travel. As before all costs are expressed in 1989 prices.

Management	Average costs (£)
One daycare visit	
Hotel care (5 h visit including lunch)	10·82
Nursing care (frequent BP measurement)	26·57
Medical care (review)	1·17
Tests*	21·50
Total	60.06
One week as inpatient	
Hotel care	94·22
Nursing care	281·26
Medical care	80·50
Tests†	63·91
Weekly total	519·89
Average daily	74·27
Domiciliary midwife BP check	
Nursing care	5·03
Travel for midwife	1·50
Total	6·53

*Full blood count, platelets, urea and electrolytes, cardiotocograph and ultrasonography where appropriate.

†Full blood count, platelets, urea and electrolytes, liver function tests, 24 h urine collection and cardiotocograph twice weekly. Ultrasonography fortnightly.

Received 25 July 1991
Accepted 16 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 464–468

FETAL AND NEONATAL MEDICINE

Fetal breathing movements in oligohydramnios are not increased by amnioinfusion

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ABSTRACT

Objective To determine whether fetal breathing movements (FBM) in pregnancies with oligohydramnios change with restoration of amniotic fluid volume.
Design A prospective experimental study.
Setting Fetal Medicine Unit, tertiary referral hospital.
Subjects 16 women with singleton pregnancies complicated by severe oligohydramnios.
Interventions: Restoration of amniotic fluid volume by transabdominal amnioinfusion. Controls comprised pregnancies in which infused fluid leaked vaginally, so that oligohydramnios was not corrected.
Main outcome measures Change in total breathing movements, change in FBM incidence derived from 40 min recordings immediately before and after amnioinfusion.
Results There was no significant difference in the change in total breathing movements or in the change in incidence of FBM between the 10 pregnancies in which amniotic fluid volume was restored, and the other six in which fluid leaked after infusion and volume was not restored. In both groups, there was no significant change with infusion in number of FBM (mean change −72, 95% CI −218 to +74 in the fluid-retained group and −64, 95% CI −273 to +145 in the fluid-leaked group) and incidence of FBM (median change −2·5%, range −27 to +10 in the fluid retained group and −4·5%, range −34 to +15 in the fluid-leaked group).
Conclusions This study suggests that restitution of amniotic fluid volume in human pregnancies complicated by severe oligohydramnios does not acutely alter the incidence of FBM. These data support an increasing literature suggesting that impairment of fetal breathing is not the mechanism for oligohydramnios-related pulmonary hypoplasia.

Pulmonary hypoplasia is found in 15% of perinatal necropsies (Wigglesworth & Desai 1982), and oligohydramnios is the most common aetiology. Although removal of amniotic fluid has been shown to produce pulmonary hypoplasia in experimental studies (Adzick *et al.* 1984; Moessinger *et al.* 1985), the mechanism by which oligohydramnios inhibits lung growth is not understood.

Inhibition of fetal breathing movements (FBM) is known to cause pulmonary hypoplasia, both from animal studies (Alcorn *et al.* 1980; Liggins *et al.* 1981), and from reports of human fetuses with neurological deficit (Dornan *et al.* 1984). In prolonged oligohydramnios, the fetus is widely held to be compressed, on the basis of its characteristic flattened facies and positional limb deformities (Perlman & Levin 1974; Thomas & Smith 1974). Extrathoracic compression inhibiting FBM has thus been suggested as the cause of oligohydramnios-related pulmonary hypoplasia (Gruenwald 1957; Wigglesworth *et al.* 1977). In this regard, Blott *et al.* (1987, 1990) recently noted in oligohydramnios secondary to preterm prelabour rupture of the membranes that FBM were absent in fetuses subsequently shown to have pulmonary hypoplasia, and present in those which survived the neonatal period. These findings were directly contradicted by another group who found the incidence of FBM in fetuses with oligohydramnios and pulmonary hypoplasia to be the same as in controls, and greater than in those with oligohydramnios and no hypoplasia (Fox & Moessinger 1985; Moessinger *et al.* 1987). This disparity has been suggested as simply due to different definitions of FBM (Greenough *et al.* 1988). Nevertheless oligohydramnios produces pulmonary hypoplasia in sheep without diminishing FBM (Dickson & Harding 1991), whereas numerous human pregnancies have been reported with FBM continuing in the presence of oligohydramnios-related hypoplasia (Kilbride *et al.* 1988; Van Eyck *et al.* 1990).

Whether FBM are inhibited in oligohydramnios remains controversial. The aim of this study was to determine whether FBM changed with restoration of amniotic fluid volume in human pregnancies complicated by oligohydramnios.

Subjects and methods

Sixteen women with severe oligohydramnios in singleton

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pregnancies scheduled to undergo clinically-indicated diagnostic amnioinfusion between 17 and 31 weeks (median 23) gave written informed consent to inclusion in this study, approved by the institutional ethics committee. Transabdominal amnioinfusion with 150–350 ml warmed normal saline (25–50 ml/min) was performed without sedation under ultrasound control as described previously (Fisk *et al* 1991). Fetal blood sampling was also performed in 13 pregnancies for rapid karyotyping.

The deepest vertical pool, amniotic fluid index (AFI) (Moore & Cayle 1990) and amniotic pressure (Fisk *et al* 1990) were measured before and immediately after infusion. End-diastolic frequencies were observed in the umbilical artery Doppler waveforms of all fetuses, both before and after the procedure, excluding significant fetal hypoxaemia and acidaemia (Nicolini *et al.* 1990). The aetiology of oligohydramnios was classified after infusion as follows: prolonged rupture of the membranes in eight, bilateral fetal renal pathology in two, intrauterine growth retardation in three, and idiopathic in three.

FBM were recorded continuously for 40 min before and 40 min immediately after amnioinfusion. No patient smoked or consumed alcohol within 1h of recording. Glucose loading was not performed in view of (i) glucose loading not having an effect on FBM until ⩾ 30 weeks (Trudinger & Knight 1980; Natale *et al* 1988) and (ii) the difficulty standardizing the pre- and post-infusion recordings for maternal glucose. With the woman lying semi-recumbent, a realtime ultrasound transducer was used to identify the fetal thorax and abdomen in a longitudinal plane. Care was taken to avoid undue compressive force on the fetal thorax by supporting the operator's arm during the recording on pillows level with the vertical height of the fundus. Each fetal breathing movement, defined as inward movement of the thorax with paradoxical outward movement of the abdominal wall, was recorded by means of a manually operated tone generator onto audiotape. All recordings were made by the same person (NMF).

We have shown recently that a proportion of women with severe oligohydramnios will leak fluid immediately after amnioinfusion (Fisk *et al.* 1991), reflecting pre-existing amniorrhexis. In order to control for any effect of amnioinfusion on FBM, we compared the change in FBM with infusion in pregnancies in which fluid was retained and oligohydramnios corrected with those in which the infused fluid leaked before the post-infusion recording, thus failing to correct oligohydramnios.

The audiotape was replayed into the input port of a BBC microcomputer, which quantified the intervals between initiation of tone signals at 0·5 s intervals. Digitized data were then analysed for total breathing movements and the occurrence of FBM using the two definitions (Greenough *et al.* 1988). In line with convention, an episode of FBM was only considered to have occurred when several movements were noted within a minimum time frame or epoch; this was done to exclude isolated diaphragmatic movements and hiccoughs (Pillai & James 1990). Under definition A, an epoch of fetal breathing comprised continuous breathing movements for ⩾ 60s in the absence of any apnoeic interval >6 s (Blott *et al* 1987, Greenough *et al.* 1988). With definition B, an epoch began whenever three breathing movements occurred within a 6-s window, and ended whenever there were fewer than three breathing movements within any subsequent 6-s window, (Moessinger *et al.* 1987). The incidence of FBM was thus defined as the percentage of time spent in FBM epochs.

Changes in variables with infusion were expressed as the postinfusion value minus the preinfusion value. Non-parametric statistics were used when non-Gaussian distributions were evident on histograms. Relations between variables were assessed by Pearson and Spearmann correlation coefficients for parametric and non-parametric data as appropriate. Comparisons were by *t*-testing (paired or unpaired) for normally distributed data, linear regression was also used; for non-normally distributed data Wilcoxon or Mann-Whitney tests were used as appropriate.

Results

Before infusion, the deepest pool and AFI were ⩽ 1·2 and ⩽ 2·3 cm respectively. Vaginal fluid leakage was noted during the procedure in 6 of the 16 patients. No patient in the fluid-retained group ($n = 10$) leaked within 4 h of infusion, whereas further leakage was noted during the postinfusion recording in 4 of 6 in the leakage group. Gestational age was similar in the fluid retained (median 23·3 weeks, range 8–31) and fluid-leakage groups (median 21 weeks, range 17–28). In the fluid-retained group, amnioinfusion significantly increased amniotic fluid volume (mean change in AFI = 10·0 cm, 95% confidence intervals [CI] 8·7 to 11·2, paired, *t*-test $P < 0{\cdot}001$), whereas in the fluid leakage group, only a minimal increase was observed (change in AFI = 1·8 cm CI 0·2 to 3·4, paired *t*-test $P = 0.08$). The deepest pool and AFI postinfusion were both significantly greater in the fluid-retained (median 4·0 range 2·9–4·8, and median 10·6 range 9·1–13·4 respectively) than the fluid leakage group (median 1·2, range 0·6–2·9, Mann-Whitney $P < 0{\cdot}01$ and median 2·1, range 0.6–5·9, Mann-Whitney $P < 0{\cdot}01$).

The total number of FBM per recording did not change significantly with amnioinfusion, either in the fluid-retained or the fluid-leakage group (Table 1). Most fetuses had no definition A FBM epochs detected either before ($n = 10$) or after infusion ($n = 12$). All six fetuses with definition A epochs recorded before the infusion had none after the infusion, whereas all four fetuses with definition A FBM epochs present after infusion did not have any before the infusion. In contrast, all but one fetus had definition B FBM epochs present before the infusion and all but two after infusion (Fig. 1). There was no significant change in incidence in FBM with infusion in either the fluid retained or leaked group, using definition A and definition B.

In the fluid retained group, there was no significant correlation between the change in incidence of FBM (definition B) and gestational age, the change in AFI, the change in deepest pool, or volume infused. However, the change in incidence (definition B) increased significantly with increasing change in amniotic pressure ($y = 25{\cdot}0 + 8{\cdot}8\,x$, $R^2 = 0{\cdot}94$, $P < 0{\cdot}001$, where y = the change in incidence of FBM and x = the change in amniotic pressure, Fig. 2); thus the incidence of FBM decreased when the rise in amniotic pressure was ⩽3 mm Hg, but otherwise increased slightly. No such correlation was observed in the fluid leakage group. Multiple linear regression indicated that the change in incidence of FBM (definition B) in

Table 1. The effect of amnioinfusion on the number and incidence of fetal breathing movements (FBM) using two different definitions (A = Greenough *et al.* 1988; B = Moessinger *et al* 1987)

	Fluid retained (n = 10)	Fluid leaked (n = 6)	Significance (retained *vs* leaked)
Total FBM (no)	Mean (95% CI)	Mean (95% CI)	
Preinfusion	238 (129 to 347)	241 (91 to 391)	NS (unpaired *t*-test)
Postinfusion	173 (127 to 219)	178 (32 to 323)	NS (unpaired *t*-test)
Change with infusion*	−72 (−218 to +74)	−64 (−273 to +145)	NS (unpaired *t*-test)
	NS (paired *t* test)	*NS* (paired *t*-test)	
Definition A (%)	Median (range)	Median (range)	
Preinfusion	0 (0 to 7)	0 (0 to 11)	NS (Mann-Whitney)
Postinfusion	0 (0 to 3)	0 (0 to 12)	NS (Mann-Whitney)
Change with infusion*	0 (−7 to +3)	0 (−11 to +12)	NS (Mann-Whitney)
	NS (Wilcoxon)	*NS* (Wilcoxon)	
Definition B (%)	Median (range)	Median (range)	
Preinfusion	8·5 (0 to 28)	5·5 (0·3 to 34)	NS (Mann-Whitney)
Postinfusion	5·5 (1 to 15)	2·5 (0 to 16)	NS (Mann-Whitney)
Change with infusion*	−2·5 (−27 to +13)	−4·5 (−34 to +15)	NS (Mann-Whitney)
	NS (Wilcoxon)	*NS* (Wilcoxon)	

NS = no significant difference between fluid retained and fluid leaked groups.
NS = not significantly different from zero.
* = indicates the mean of each individual patient's change with infusion.

the fluid-retained group was highly significantly correlated ($P < 0{\cdot}001$) with both the pre- and postinfusion amniotic pressures. However, the incidence of FBM (definition B) did not correlate significantly with baseline amniotic pressure, either before or after amnioinfusion. There was no significant correlation between the change in amniotic pressure and gestational age, volume infused, AFI or deepest pool, either as the preinfusion, postinfusion, or change in value with amnioinfusion.

Discussion

This study indicates that restitution of amniotic fluid volume in human pregnancies complicated by severe oligohydramnios does not acutely alter the incidence of FBM.

We chose to study the acute effect only because (i) this standardized for confounding variables by minimizing the interval between recordings, and (ii) most were outpatients referred long distances to our institution. We considered the possibility that some aspect of the procedure other than restitution of amniotic fluid volume might acutely prevent any increase in FBM, which may have been detectable later. Prostaglandins are known to inhibit FBM (Kitterman *et al.* 1983), and theoretically, penetrating the uterus with a needle may have precipitated local prostaglandin release. However, amniocentesis has been shown not to have any immediate effect on the incidence of FBM (Hill *et al.* 1979).

Observation periods of 30–100 min have been used pre-

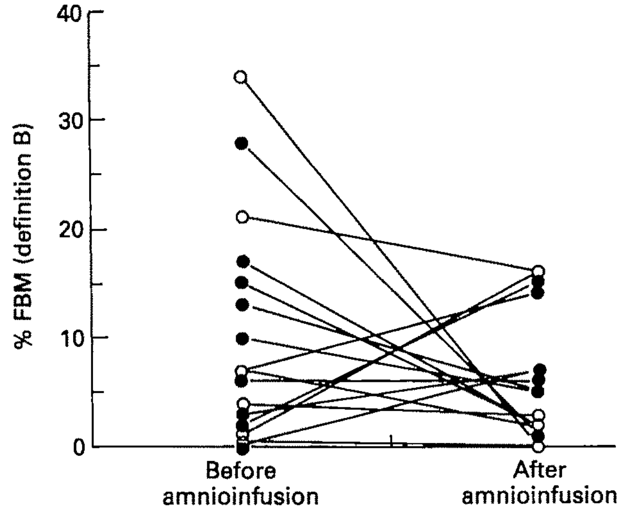

Fig. 1. The incidence of FBM (=% of time spent in FBM epochs) using definition B (Moessinger *et al.* 1987) before and after amnioinfusion in 16 pregnancies. ○ pregnancies that leaked; ● pregnancies that retained infused fluid.

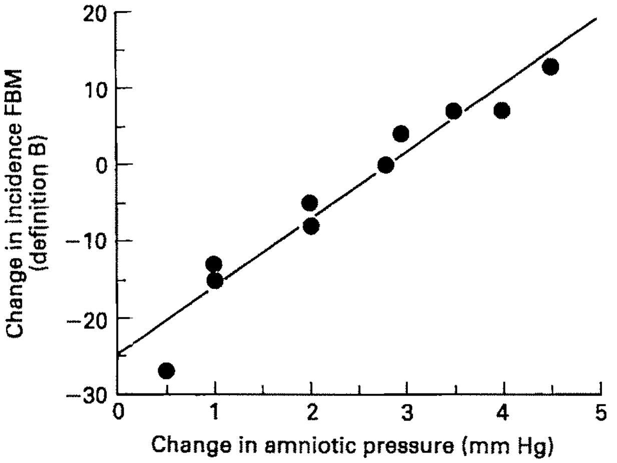

Fig. 2. The association between the change in FBM incidence (= % of time spent in FBM epochs according to definition B) and the change in amniotic pressure in amnioinfusions in which fluid was retained.

viously to study human FBM (Roberts *et al.* 1980; Pillai & James 1990). We chose a relatively short interval of 40 min, out of concern for maternal tolerance of two recordings and an invasive procedure in the one session. The considerable variance in FBM incidence noted in this study has also been reported by others using longer recording periods (Pillai & James 1990), suggesting that increasing the observation period is unlikely to have had a major influence on our results.

Our data agree with other publications suggesting that impairment of fetal breathing is not the mechanism for oligohydramnios-related pulmonary hypoplasia. Fetal breathing movements continue during acute (Moessinger *et al.* 1985) and chronic oligohydramnios (Dickson & Harding 1991) in sheep. Experimental inhibition of FBM in addition to oligohydramnios produces more severe pulmonary hypoplasia than oligohydramnios alone (Adzick *et al.* 1984). Furthermore extrathoracic compression impairing FBM is considered unlikely as (i) amniotic pressure is low in severe oligohydramnios (Fisk *et al.* 1990); (ii) the major component of FBM is mediated by diaphragmatic rather than intercostal muscles (Dawes *et al.* 1980), and (iii) experimental abdominal compression has no effect on lung development (Sauer *et al.* 1987).

The group which claimed FBM were 'absent' in fetuses with pulmonary hypoplasia secondary to prolonged ruptured membranes (Blott *et al* 1987), later elaborated that this meant continuous epochs of FBM lasted < 60 s (Greenough *et al* 1988), a definition used in the third trimester (Roberts *et al.* 1980; Vintzileos *et al.* 1983). The incidence of FBM, however, is considerably lower in the mid-trimester, when the risk of oligohydramnios-related pulmonary hypoplasia is greatest (Wigglesworth & Desai 1982). Using their definition, FBM were 'absent' in most fetuses in our study, both before and after infusion, in keeping with our experience in mid-trimester fetuses with normal amniotic fluid volume (unpublished observations). Pillai & James (1990) in a recent longitudinal study, involving over 400 h of recording, found that more than 75% of fetuses ⩽ 28 weeks did not breathe in epochs of ⩾ 60 s. The 60 s definition is thus inappropriate in the mid-trimester, when fetuses at risk of oligohydramnios-related pulmonary hypoplasia are most likely to be assessed.

The factors determining fetal breathing are poorly understood. Using the more appropriate definition B, we found that the incidence of FBM decreased when the rise in amniotic pressure was ⩽ 3 mm Hg, but otherwise increased slightly (Fig. 2). This presumably reflects some as yet uncharacterized fetal response to the amnioinfusion-induced rise in amniotic pressure (Fisk *et al.* 1990), since FBM incidence, either before or after infusion, did not appear determined by amniotic pressure. We have hypothesized previously that alterations in amniotic pressure may alter the aveolar-amniotic pressure gradient which determines fetal lung liquid escape (Nicolini *et al.* 1989). As lung liquid loss into the amniotic cavity is greater during FBM than during apnoea (Harding *et al.* 1984), this response may reflect an adaption to altered alveolar-amniotic pressure to maintain fetal lung volume.

Acknowledgments

N.M.F. was supported by a Joseph Foreman Fellowship from the Royal Prince Alfred Hospital, Sydney, Australia. J.V. was the recipient of an RNSH Medical Board Centenary Fellowship from the Royal North Shore Hospital.

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Received 23 May 1991
Accepted 13 February 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 469–474

FETAL AND NEONATAL MEDICINE

Detection of small-for-gestational-age fetuses by ultrasound screening in a high risk population: a randomized controlled study

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ABSTRACT

Objective To assess the value of fetal weight estimation during routine third trimester ultrasound examinations for the identification of small-for-gestational-age (SGA) fetuses, to promote active pregnancy management and so reduce perinatal morbidity.
Design A prospective controlled randomized study.
Setting Outpatient clinic at the Department of Obstetrics, Herlev University Hospital, Denmark.
Subjects One thousand pregnant women considered at risk were selected consecutively from April 1985 to September 1987 and randomized to either a revealed-results group or a withheld-results group.
Intervention All the women had an early ultrasound examination for estimation of gestational age. Both groups had routine ultrasound estimates of fetal weight after 28 weeks and then every third week until delivery. The results were available for clinical use only in the revealed group.
Main outcome measures Number of interventions during pregnancy (admission to hospital, elective delivery), emergency intervention during labour, and fetal outcome.
Results Revealing the results of ultrasound estimates of fetal weight for gestational age during the third trimester resulted in statistically significantly increased diagnosis of SGA fetuses, of elective deliveries based on this diagnosis, and of healthy preterm babies admitted to the neonatal care unit, but no detectable overall improvement in weight for gestational age at birth, or in neonatal morbidity or mortality.
Conclusion This method of screening improved the diagnosis of SGA fetuses, but this was not followed by improved fetal outcome.

Prenatal diagnosis of suspected fetal growth retardation is still one of the main problems in modern obstetrics. Several techniques have been proposed, many of which have been incorporated into routine practice without being assessed in controlled studies. Such studies are important as clinical action based on the results of these diagnostic techniques may do harm. In prenatal medicine, this is of particular importance, since most pregnancies will have a normal outcome whether they are tested or not.

Fetal growth retardation may be suspected in fetuses when fetal dimensions follow a low centile or fail to increase appropriately. The latter group includes some fetuses with appropriate-weight-for-gestational age (AGA). In routine clinical practice, the reliable detection of abnormal fetal growth in AGA fetuses is not realistic, but by using ultrasound fetobiometric measurements, it may be possible to distinguish between the two growth patterns.

Ultrasound examination has been used increasingly for the diagnosis of fetal growth retardation. Randomized trials by Neilson *et al.* (1984), Secher *et al.* (1986) and Bakketeig *et al.* (1984), designed to investigate the efficacy of. ultrasound screening, have demonstrated sensitivities of 94%, 38%, 25%, respectively, in identifying small-for-gestational-age (SGA) fetuses but these studies found no differences in interventions during pregnancy nor in fetal outcome between study and control groups. In a briefly reported randomized study by Eik-Nes *et al* (1984), identification of abnormal fetal growth in the screened group resulted in more active obstetric intervention. This involved more postnatal days in hospital for dysmaturity but it was also associated with somewhat fewer deaths associated with growth retardation in this group.

The most significant question in monitoring fetal growth is: does the use of the test during pregnancy improve fetal outcome? The first step in this consideration must be to assess the diagnostic capabilities of the test, the next step is to examine how the results of the test are used in clinical practice.

When fetal growth retardation is suspected, clinical intervention is based on suspicion of SGA and does not usually occur when the fetus is judged to have normal weight. The

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present study was designed to investigate the efficacy of our standard antenatal care in terms of identifying SGA fetuses, with and without ultrasound biometric measurements. By adding ultrasound screening we expected improved selection of SGA fetuses and thereby a more correct use of elective interventions during pregnancy, a reduction of acute interventions during labour, and improved fetal outcome. The socio-economic aspects of our findings will be reported elsewhere.

Subjects and methods

Herlev University Hospital serves about 1700 to 1800 unselected (except for maternal diabetes and Rhesus immunizations being referred elsewhere) pregnancies per year in a geographically well-defined area. During the period of the study there were 4350 deliveries. Since January 1983, all women attending the Department of Obstetrics have been offered an early ultrasound for estimation of gestational age, identification of twins, and detection of malformations.

From April 1985 all pregnant women in the antenatal clinic entered the study consecutively if they had at least one of the risk factors or one of the signs of pregnancy complications listed in Table 1. By September 1987, 1000 women had been entered.

The sample size of 1000 was chosen because, in a retrospective pilot survey of 1000 pregnancies, the frequency of SGA infants in the subgroup with risk factors was 20%. The decision on sample size was also based on the practical limitations of conducting the trial.

Allocation

The women were allocated randomly to attend either the revealed group or the withheld group by drawing a sealed numbered (1–1000) envelope. This number was assigned to the woman for the duration of the trial to ensure complete follow-up. Based on random numbers (Geigy Scientific Tables) the envelopes contained information on the group to which the woman was to be allocated (even numbers = revealed group, odd numbers = withheld group).

Table 1. Risk factors at trial entry in women allocated to the revealed-results and the withheld-results group

Risk factor	Revealed (n = 484)	Withheld (n = 481)
Previous perinatal death	47	37
Previous SGA infant	42	43
Previous major malformation	10	12
Previous perinatal brain damage	4	3
Previous placental abruption	9	7
Previous placental insufficiency	22	18
Essential hypertension	7	8
Previous pre-eclampsia	47	37
>15 cigarettes per day	160	173
Previous preterm delivery	18	30
Maternal cardiac/renal disease	10	3
Chronic bowel disease	9	7
Haemorrhage in first two trimesters	144	116
Low uterine height measurements	137	134
Hypertension	16	11
Pre-eclampsia	34	32
Urinary tract infection	19	13
Haemorrhage in third trimester	38	21
Maternal low weight-gain	21	20
Abnormal serum-oestriol	50	56
Abnormal human placental lactogen	63	63
Alcohol or drug abuse	9	12

Of the 1000 women allocated, 35 were excluded, five because of twins (two in the revealed group and three in the withheld group), 14 because they were incorrectly allocated twice (seven in each group), and 16 because they miscarried (nine in the revealed group and seven in the withheld group). Thus the study comprised 965 women; 484 in the revealed group and 481 in the withheld group. Seventy-six (7·6%) of the allocated women subsequently decided not to participate in the study (40 in the revealed group and 36 in the withheld group).

Informed consent was obtained before the first scheduled ultrasound examination was performed at 28 weeks. The study was approved by the local ethics committee.

Ultrasound examination

Ultrasound examinations were carried out by four experienced ultrasonographers supervised by one of the authors (T.L.). Dynamic ultrasound equipment was used and sound velocity in tissue was assumed to be 1540 m/s. Biparietal diameter was measured, with electronic calipers, at right angles to the longitudinal axis of the skull, from the outer edge of the anterior to the inner edge of the posterior skull wall at the level of the thalami. Abdominal diameter (AD) was measured at right angles to the fetal aorta or spine at the level at which the umbilical vein joins the portal sinus. The antero-posterior and orthogonal diameters were measured from the outer limit of the abdominal circumference (AC). The geometric mean was used to calculate AC from AC = π AD. The median of three measurements was used.

A personal computer with software developed for this study (Larsen & Hannibal 1988) was used for estimation of the following variables at each scheduled examination: (1) expected date of delivery calculated from early biparietal diameter (Persson *et al.* 1986); (2) estimate of gestational age calculated from early biparietal diameter; (3) the ultrasound estimate of fetal weight calculated from biparietal diameter and AC using the equation of Warsof *et al.* (1977); (4) normal fetal weight for actual gestational age using a Danish reference curve (Secher *et al.* 1986); and (5) percentage deviation of the ultrasound estimate of fetal weight from normal fetal weight. For women allocated to the revealed group, an updated form with all ultrasound measurements and estimates was released for clinical use after each ultrasound examination.

Calculation of fetal weight

In a pilot study we found acceptable agreement between actual birthweight and ultrasound estimated fetal weight using the equation of Warsof *et al.* (1977), therefore, we used this equation in the present study. The inter- and intra-observer variations were 4·6% and 2·9%, respectively (Larsen *et al.* 1990). Fetuses or infants with weight below the 10th centile according to a Danish reference curve (Secher *et al.* 1986) were designated SGA.

In both groups, ultrasound examinations were scheduled at 28, 31, 34, 37, 39 and 41 weeks gestation, or until delivery. Women entering the study after 28 weeks gestation followed this schedule from the time of entry. In the revealed group the results of the ultrasound estimates of fetal weight were made available to the clinicians caring for women, but in the withheld group only the results of the early routine ultrasound examination, with an estimate of the gestational age, were disclosed.

Clinical findings, other than those based on ultrasound biometric measurements, were made available in both groups (including malformations, placenta previa, oligohydramnios). During the study, ultrasound estimates of fetal weight were only provided for pregnancies included in the study. To ensure comparability in the number of ultrasound examinations between the two groups, fetal weight was estimated only at scheduled times and not on demand.

According to the protocol, the clinician could obtain information on ultrasound estimates of fetal weight in the withheld group under 'special obstetric circumstances'. This exception required permission from one of two independent gynaecologists in the department. Permission was, however, never granted.

The routine consultations and investigations for this group of risk pregnancies were numerous (Table 2) and remained unchanged during the period of study.

The following details were recorded prospectively for each woman in the study: risk factors, suspicion of SGA during pregnancy, suspicion of SGA sustained, clinical consequences, i.e., admission to hospital, intervention during pregnancy and delivery, and the indications for intervention.

Assessment of neonatal status

Although those assessing neonatal status (S.P. and G.G.) were not blind to group allocation, they were unaware of the ultrasound results relating to the babies they examined.

Statistical methods

Differences between groups were tested using ANOVA including the Student-Newmann-Keuls procedure. χ^2 or Fisher's exact test were used to test differences in 2 × 2 tables. Odds ratios were calculated using EpiInfo 5·0 (WHO). The Wilcoxon rank sum test was used to compare data not normally distributed. A 95% confidence limit was chosen.

Results

Comparability

At trial entry the number of women, dropouts, frequency of risk factors, maternal age, and height, parity and infants' sex were comparable in the two groups (Tables 1 and 3). Although the mean numbers of hormone measurements was somewhat higher in the revealed group (7·2 per pregnancy) than in the withheld group (6·6 per pregnancy), the distributions of abnormal test results (uterine height measurements, serum oestriol and human placental lactogen hormone measurements) were similar (Table 1).

The number of ultrasound examinations at 28, 31, 34, 37, 39 and 41 weeks, the scheduled weeks of gestation, was 304, 332, 374, 336, 186 and 32, respectively, in the revealed group, and 313, 327, 348, 355, 226, and 28, respectively, in the withheld group. On average, 3·2 ultrasound examinations were performed per pregnancy in the revealed group compared with 3·3 in the withheld group.

Diagnoses of SGA fetuses

The possibility that fetuses were SGA was raised (and sustained) by the clinician providing clinical care in 96 pregnancies in the revealed group (20%) and in 71 in the withheld group (15%) ($P = 0{\cdot}04$).

Intervention during pregnancy and delivery

There were no statistically significant differences in obstetric management between the two groups, except for a longer mean antenatal stay in hospital in the revealed group (7·2 days *vs* 5·9 days) ($P = 0{\cdot}04$). The frequency of elective intervention during pregnancy was similar in the two groups but the diagnosis of SGA fetus was used significantly more often as an indication for induction of labour in the revealed group than in the withheld group. There were no differences for other diagnoses for interventions during pregnancy between the two groups.

The frequency of emergency interventions during labour and delivery was similar in the two groups. Suspicion of intrauterine asphyxia was used as an indication for intervention in 43 women in the revealed group compared with 58 in the withheld group (not significant).

Fetal outcome

The outcome of one pregnancy in the revealed group is unknown because the woman emigrated before delivery.

Table 2. Clinical routines for pregnancies in which the fetus is considered to be at risk

	Gestational age (weeks)															
Examination	10	16	20	24	26	30	33	35	36	37	38	39	40	41	42	Total number
GP	+				+			+								3
Midwife			+	+		+	+			+		+		+		7
Obstetrician		+							+		+		+		+	5
Uterine height		+	+	+	+	+	+	+	+	+	+	+	+	+	+	14
E_2 and hPL						+	+		+		+			+	+	6
Ultrasound		+														1

Abbreviations: GP, general practitioner; E_2, oestriol; hPL, human placental lactogen

Table 3. Summary of comparability of the two groups

	Revealed (n = 484)	Withheld (n = 481)
Maternal age (years)	28 (5)	28 (5)
Maternal height (cm)	167 (6)	167 (7)
Primiparae	115 (24%)	100 (21%)
Secundiparae	156 (32%)	184 (38%)
Multiparae	213 (44%)	197 (41%)
Infants' sex		
Male	239 (49%)	248 (52%)
Female	245 (51%)	233 (48%)

Results are mean (SD) or n (%) values as appropriate.

The mean birthweight was 3188 (SD 602) g in the revealed group and 3219 (SD 628) g in the withheld group (this difference was not significant). The use of ultrasound did not alter the percentage of SGA infants, which was 13% in both groups. The mean gestational age in the revealed group was 273 (SD 15) days and 274 (SD 16) days in the withheld group (not significant). The number of infants born before 37 completed weeks, or with a birthweight below 2500 g was not significantly different between the revealed and the withheld group. The number of infants with low Apgar scores or low umbilical artery pH did not differ significantly between the two groups.

Admission to the neonatal care unit (NCU) was necessary more often in the revealed group than in the withheld group (P = 0·01). This was accounted for by the hospital policy of admitting all low birthweight babies to the NCU for observation, 47 infants in the revealed group compared with 23 in the withheld group. However, there was no difference in the number of infants admitted to the neonatal intensive care unit (NICU) e.g. for respiratory distress.

There was no statistically significant difference in perinatal morbidity between the groups. Neither was there any difference in perinatal morbidity among infants with low birthweight or preterm delivery in the two groups. Of these, 12 infants in the revealed group needed intensive care versus 19 in the withheld group (not significant), of which four infants were ventilated for respiratory distress in the revealed group compared with nine infants in the withheld group (not significant). Nine of the 29 women in the revealed group and 10 of the 25 in the withheld group were delivered electively. One infant in the revealed group, born after spontaneous onset of labour at 26 weeks, had a birthweight of 972 g, developed severe respiratory distress syndrome and died at 13 days of age.

Morbidity related to causes other than malformations or asphyxia among term infants with birthweights above 2500 g (infections, respiratory problems, hyperbilirubinaemia and admission for observation) was more frequent in the revealed group (P = 0·02). This was not related to elective intervention during pregnancy or delivery, which occurred in 10 of the 25 babies in the revealed group compared with 6 of the 12 in the withheld group.

There were five perinatal deaths in the revealed group and three in the withheld group (not significant). Three infants in the revealed group and one in the withheld group had lethal congenital malformations: one had a ventricular and atrial septal defect and truncus arteriosus, not identified on ultrasound (birthweight AGA); one had bilateral renal agenesis and oligohydramnios and had been considered SGA from 28 weeks (birthweight SGA); one had a diaphragmatic hernia, pulmonary hypoplasia, and hypoplastic left ventricle (birthweight AGA). In this case, only the heart malformation was diagnosed prenatally by ultrasound. One infant in the withheld group had trisomy 13. The mother had had only an early ultrasound examination, which did not reveal any abnormality. There were two antepartum fetal deaths in the revealed group, one caused by placental abruption at 34 weeks, the other followed a

Table 4. Obstetric interventions in the two study groups

	Revealed (n = 484)	Withheld (n = 481)	Odds ratio (95% CI)
Admission to hospital before delivery	291 (60%)	269 (56%)	1·19 (0·91; 1·55)
Spontaneous delivery	260 (54%)	258 (54%)	1·00 (0·77; 1·30)
Elective interventions			
Total number	126 (26%)	122 (25%)	1·04 (0·77; 1·40)
Primary rupture of membranes	9 (2%)	13 (3%)	
Induction of labour	80 (17%)	70 (15%)	
Elective CS	37 (8%)	39 (8%)	
Induction for			
Pre-eclampsia	25 (5%)	17 (4%)	
Placental insufficiency	45 (9%)	44 (9%)	
SGA fetus	43 (9%)	19 (4%)	2·37 (1·32; 4·29)
Other*	42 (9%)	57 (12%)	0·71; (0·45; 1·10)
Emergency interventions			
Total number	98 (20%)	101 (21%)	0·96 (0·69, 1·32)
Vacuum extraction and forceps	43 (9%)	55 (11%)	
Emergency CS	55 (11%)	46 (10%)	
Indication for intervention			
Asphyxia	43 (9%)	58 (12%)	0·71 (0·46; 1·10)
Other†	56 (12%)	46 (10%)	1·24 (0·80; 1·91)

*Breech presentation, contracted pelvis, previous complicated delivery, placenta praevia, malformations, social and psychological factors.
†Placental abruption, breech presentation, cephalopelvic disproportion, dysfunctional uterine action, pre-eclampsia and placenta praevia.
Abbreviations: CS, caesarean section; 95% CI, 95% confidence interval, SGA, small-for-gestational age.

Table 5. Perinatal outcome measures in the two study groups

	Revealed (n = 484)	Withheld (n = 481)	Odds ratio (95% CI)
SGA	64 (13%)	62 (13%)	1·03 (0·70; 1·53)
Birthweight <2500 g	54 (11%)	39 (8%)	1·43 (0·91; 2·25)
Gestation <259 days	60 (12%)	43 (9%)	1·45 (0·94; 2·24)
Apgar scores ≤7			
At 1 min	48 (10%)	55 (11%)	0·85 (0·55; 1·31)
At 5 min	22 (5%)	22 (5%)	0·99 (0·52, 1·89)
Cord pH≤ 7·15	26 (5%)	29 (6%)	0·91 (0·51; 1·62)
Neonatal care*			
Total number	75 (15%)	48 (10%)	1·66 (1·11, 2·49)
Admitted to NCU	47 (10%)	23 (5%)	
Admitted to NICU	28 (6%)	25 (5%)	
Neonatal morbidity*			
Total number	66 (14%)	46 (10%)	1·50 (0·99, 2·28)
In relation to			
Malformations	5	1	
Asphyxia	7	8	
Low BW or preterm birth	29 (6%)	25 (5%)	
Other causes	25 (5%)	12 (2%)	
Perinatal death			
Total number	5 (1%)	3 (1%)	1·67 (0·35; 8·83)
Stillbirths	2	1	
Congenital malformations	3	1	
Immaturity	0	1	

*Excluding perinatal deaths.
Abbreviations: NCU, neonatal care unit; NICU, neonatal intensive care unit. SGA, small-for-gestational age; BW, birthweight; 95% CI, 95% confidence interval.

violent attack on the woman at 37 weeks gestation (both stillbirths had AGA birthweights). In one infant in the withheld group the scheduled ultrasound examination at 28 weeks revealed a fetal weight deviation of –42% but also a myelomeningocele and encephalocele. As agreed in the protocol, this observation was revealed, labour was induced, and the infant was stillborn. One infant in the withheld group was born by caesarean section because of placental abruption at 32 weeks and died at three days of age from severe respiratory distress syndrome (birthweight AGA).

Subgroup analyses of SGA infants

Forty-three of the 64 (67%) SGA infants in the revealed group were suspected prenatally by the routine clinician compared with 23 of the 62 (37%) in the withheld group (χ^2 = 10·3, P = 0·001). Among 889 women who had least one ultrasound examination after 28 weeks, 159 (18%) had at least one fetal weight estimate below the 10th centile and this occurred also in 84 (73%) of 117 SGA infants.

Table 6. Obstetric interventions in pregnancies with SGA infants

	Revealed (n = 64)	Withheld (n = 62)	P value
Admission to hospital before delivery	53 (83%)	38 (61%)	0·01
Spontaneous delivery	23 (36%)	24 (39%)	>0·05
Elective interventions			
Total number	33 (52%)	21 (34%)	0·04
For SGA fetus	26 (41%)	7 (11%)	0·0004
Emergency interventions			
Total number	13 (20%)	24 (39%)	0·04
For asphyxia	9 (14%)	21 (34%)	0·02

The number of fetuses diagnosed as SGA but having a birthweight above the 10th centile was not statistically significantly different between the revealed and withheld groups. Thus the significantly increased predicted number of SGA infants in the revealed group was not associated with an increased number of suspected SGA fetuses who had AGA birthweights.

Women in the revealed group, who were admitted to hospital during pregnancy, gave birth to 53 of the 64 (83%) SGA infants, compared with 38 of the 62 (61%) SGA infants in the withheld group (P = 0·01). The increased number of days in hospital in the revealed group is ascribed to the subgroup of women who subsequently gave birth to SGA infants (average 10·3 days in the revealed group compared with 7·0 days in the withheld group P = 0·03).

Suspicion of SGA fetuses led to significantly more SGA infants being born electively in the revealed group (33 *vs* 21; P<0·04).

Of the SGA infants who were born after emergency intervention during labour because intrauterine asphyxia was suspected, nine were born in the revealed group compared with 21 in the withheld group (P = 0·02).

Within the subgroup of SGA infants the mean birthweight was 2410 (SD 397) g in the revealed and 2518 (SD 488) g in the withheld group (not significant). The mean gestational age was 271 (SD 17) days in the revealed group and 273 (SD 21) days in the withheld group (not significant). There were also no statistically significant differences in Apgar scores, cord pH ≤7·15 or in the number of infants admitted to the neonatal care unit between the two groups.

Discussion

This controlled study shows that the use of ultrasound significantly improved the prenatal detection of SGA fetuses. This led to more specific selection of pregnancies complicated by SGA fetuses for prenatal admission to hospital. However, the increased use of hospital admission in the revealed group neither reduced the number of SGA infants, nor increased the birthweight. This is in accordance with Laurin & Persson (1987), who found no effect from bed rest on fetal weight or fetal morbidity in pregnancies suspected of SGA fetuses.

It is believed and has been shown by Campbell *et al* (1982) that ultrasound examination has a positive influence on the pregnant woman (seeing her fetus) and may stimulate to change to a healthier lifestyle. However, in our study, repeated ultrasound examinations and the relevant information given to the women with impaired fetal growth was not followed by improved fetal growth. Thus, due to lack of effective treatment, the improved diagnosis of SGA fetuses cannot at present be expected to be translated into improved fetal growth.

When ultrasound results were available, the diagnosis of an SGA fetus was used significantly more often for induction of labour. This difference caused more specific induction of labour in pregnancies resulting in SGA infants. This is important since, at present, delivery of these pregnancies seems to be the only way to improve fetal outcome. It is interesting that the increased rate of labour induction in the revealed group of SGA fetuses was associated with a significantly lower rate of emergency interventions. The contrary is generally reported (Tew 1986; Belfrage *et al.* 1987). This finding may be a positive result of a better fetal growth monitoring followed by the more active element of management.

Admission to hospital did not seem to alter the occurrence of SGA infants at birth but allows close monitoring of the fetus by stress or non-stress cardiotocography (CTG). The indication for interventions following pathological CTG was registered as threatening asphyxia in this study. The decreased frequency of asphyxia as an indication for emergency interventions in the revealed group with a higher rate of admission to hospital indicates that the closer monitoring during admission did not result in action based on increased CTG monitoring. This suggests that women suspected of having a fetus with intrauterine growth retardation can be monitored as outpatients.

In our department, post-term pregnancy in itself is not accepted as an indication for induction of labour, this is done only when placental insufficiency is also suspected. Since early ultrasound examination was available in both groups we did not expect, nor did we find, any differences between the groups in the number of pregnancies delivered for placental insufficiency in post-term pregnancies.

A difference in mortality was neither expected nor found in this relatively small study. Four of eight perinatal deaths were due to severe malformations. None of these was identified by the early ultrasound examination. However, the scheduled ultrasound examination after 28 weeks revealed severe malformations in two pregnancies, and appropriate intervention was instituted. None of the three infants who died without malformations was SGA, demonstrating that the mortality associated with SGA infants is so low with standard care that a very much larger trial would be required to show any benefit of fetal weight estimation on mortality.

In our department it is policy that gestational age less than 37 weeks results in observation in the neonatal care unit. Thus, active management in the revealed group resulted in more admissions to the neonatal ward because of preterm birth. This was also the finding of Eik-Nes *et al.* (1984) and Bakketeig *et al.* (1984). The greater number of infants admitted in the revealed group was accounted for by the increased number of healthy low-birthweight infants.

A cost-effectiveness analysis based upon the present data should be carried out before adopting routine ultrasound examinations during the third trimester.

Acknowledgments

The study was supported by grants from 'Ville Heises Legat' (26/89), Sygekassernes Helsefond (37/89), Dronning Louises Børnehospitals Forskningsfond (17/85 and 16/86), and Lundbeckfonden (147/88).

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Received 15 February 1990
Resubmitted 7 June 1991
Accepted 22 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 475–478

FETAL AND NEONATAL MEDICINE

Sonographic estimation of fetal weight in diabetic pregnancy

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ABSTRACT

Objective To investigate whether fetal weight estimation by ultrasound in diabetic pregnancy might be based upon fetal abdominal circumference (AC) alone.
Design A retrospective study.
Setting Diabetes Center, Rigshospitalet and Ultrasound Laboratory, Glostrup Hospital, Copenhagen.
Subjects Eighty-six diabetic pregnant women who had an ultrasound study within 2 days before delivery.
Results We assessed in 73 fetuses various formulas based upon biparietal diameter and AC against formulas based upon AC alone, and these were only marginally less effective than the more complex ones. In 86 fetuses an AC was available. These fetuses were divided into a study population and a test population. The linear model was customized for the study population. Evaluation on the test population showed that the relative error (error as a percentage of birthweight) in predicting birthweight had a standard deviation of 7·8%. The efficacy of AC in detecting fetuses >4000 g was examined in the test population: If AC>36·0 cm was chosen as criterion for macrosomia the positive and negative predictive values were 80% (8/10) and 91% (30/33), respectively.
Conclusion Formulas for estimating fetal weight in diabetic pregnancy based on AC alone are almost as effective as more complex ones. We recommend a simple linear formula of fetal weight as a function of AC.

Proper obstetric management of the pregnant diabetic woman requires an estimate of fetal weight, and especially detection of the macrosomic fetus which is important so that elective caesarean section can be considered (Mølsted-Pedersen & Kühl 1986; Coustan 1988). The most popular formulas to estimate fetal weight from ultrasound measurements have wide 95% prediction intervals of ±15 to 22% (Hadlock *et al.* 1984), and are even less precise in maternal diabetes (Benson *et al.* 1987). The formulas are usually based on measurements of the fetal head, such as the biparietal diameter (BPD) or head circumference, and abdomen, such as the abdominal circumference (AC), and occasionally femur length, which, however, is not measured routinely by us.

Since the macrosomic fetus associated with a diabetic pregnancy is characterized by a big abdomen (excess subcutaneous adipose tissue and big liver) rather than a big skull or long extremities (Pedersen 1977) we set out to assess current formulas for estimating fetal weight against those based on AC alone. We particularly examined the diagnostic value of AC in detecting fetuses who weighed more than 4000 g.

Subjects and methods

We examined the ultrasound reports and birthweight data from all diabetic singleton pregnancies from a 5-year period, in which BPD and AC (73 fetuses), or AC alone (13 fetuses), had been determined within 2 days before delivery. Sixty-seven women were insulin-dependent before conception, whereas 19 had gestational diabetes diagnosed during pregnancy by an oral glucose tolerance test. The birthweights ranged from 1420 g to 4895 g (mean 3343 g).

BPD was measured from the outer margin of the proximal skull table to the inner margin of the distal skull table. AC was measured at a cross-sectional scan of the fetal trunk, perpendicular to the aorta, at the level of the porto-umbilical vein complex. The circumference was traced along the outer boundary of the abdomen, from a polaroid print by means of a map measurer. All ultrasound examinations were performed by one of us (J.F.P.). The reproducibility of the AC determinations as estimated by three determinations in one day in four women showed a standard deviation of 6·1 mm for measurements 27–36 cm.

The 73 complete data-sets were used to assess three current formulas (Campbell & Wilkin 1975; Warsof *et al.* 1977; Shepard *et al.* 1982). We calculated the percent deviation 100 (predicted weight − actual weight)/actual weight, which reflects the systematic error, and the standard deviation (SD) of these deviations. The calculations were carried out for the whole series and for AC intervals. By multiple linear regres-

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Table 1. Formulas for estimating fetal weight in diabetic pregnancy and their efficacy as estimated from R^2 Original formulas of Shepard *et al.* (1982) (I), Warsof *et al* (1977) (II), and Campbell & Wilkin (1975) (III) are customized by using the 73 data set of the present study (I^a–III^a). Linear and quadratic functions of AC are also given (IV^a–V^a). Formulas III^b and IV^b are based on 43 sets of data (sample A), and their efficacy is tested on sample B

Model	Regression equation	R^2
I	Log (EFW) = 0·166*BPD + 0·046*AC – 2·646*BPD*AC/1, 000 + 1·2508	0·797
II	Log(EFW) = 0·144*BPD + 0·032*AC – 0·111*BPD^2*AC/1,000–1·401	0·801
III	LN(EFW) = 0·282*AC – 0·00331*AC^2 + 2·344	0·823
I^a	Log(EFW) = 0·2053*BPD + 0·07901*AC – 5·652*BPD*AC/1,000 + 0·7285	0·839
II^a	Log(EFW) = 0·1492*BPD + 0·04545*AC – 0·2161*BPD^2*AC/1,000 + 1·2397	0 838
III^a	Ln(EFW) = 0·2453*AC – 0·002654*AC^2 + 2·8809	0·829
IV^a	EFW = 218·4*AC – 3956	0·832
V^a	EFW = 150·7*AC + 1·033*AC^2 – 2854	0·832
III^b	Ln(EFW) = 0·3371*AC – 0·004082*AC^2 + 1·4146	0·844
IV^b	EFW = 207·4*AC – 3603	0·867

EFW = estimated fetal weight in g, BPD = biparietal diameter in cm, AC = abdominal circumference in cm. Ln is the natural logarithm, which has base e instead of base 10.

sion we also optimized the three models and compared these with linear and quadratic models based solely on AC.

Finally, we used the AC measurements alone. The 86 fetuses were ranked according to AC, and then divided, odd or even, into two groups: A, a study sample (*n* = 43, mean 3287 g, range 1490–4850) and B, a test sample (*n* = 43, mean 3399 g, range 1925–4895). We used the study sample to create optimized versions of the Campbell & Wilkin (1975) model and the linear model, and then tested the obtained formulas on sample B.

The accuracy of the different models was compared by Friedman's two-way analysis of variance performed on the percent deviations. Comparison of predictive values of a positive or negative test between different studies was performed by Fisher's exact test. A significance level of $P<0·05$ was chosen.

Results

Table 1 gives the original formulas for fetal weight estimation and those based on our own data. There is no significant difference between the accuracies of our customized formulas I^a-V^a. The efficacy of the original formulas and our customized versions is given in more detail in Table 2. The Shepard & Warsof models which use both BPD and AC are slightly better than the Campbell model, which uses only the AC, and is no better than a quadratic or a simple linear function of AC. The Campbell and linear formulas customized for population A are listed in Table 1 (III^b and IV^b), and their efficacy as tested on population B is given in Table 2.

With only one ultrasound measurement in the formula it is easier to use the ultrasound dimension directly instead of the estimated fetal weight for detecting fetuses weighing, for example, more than 4000 g. The efficacy of AC in this respect, as tested on population B, is shown in Table 3. For example, an AC>36·0 cm has a sensitivity and specificity of 73% (8/11) and 94% (30/32), respectively, and a predictive value of a positive and a negative test of 80% (8/10) and 91% (30/33), respectively. The prevalence of fetuses weighing >4000 g was 21% in sample B.

Table 2. Comparison of weight estimation in 73 (43) diabetic pregnancies The formulas are given in Table 1

	Mean percent deviation (SD)					
		Abdominal circumference (cm)				
Model	Total (*n* = 73)	25·1–30·0 (*n* = 10)	30·1–32·0 (*n* = 18)	32·1–34·0 (*n* = 17)	34·1–36·0 (*n* = 14)	36 1–39·0 (*n* = 14)
I	–4·3 (9·2)	–5·9 (10·7)	–2·5 (9·5)	–5·6 (8·9)	–5·0 (9·3)	–3·2 (7·6)
II	–8·8 (8·8)	–11·0 (10·1)	–7·4 (8·9)	–10·0 (8·5)	–9·3 (8 9)	–7 0 (7·1)
III	–4 0 (8·8)	–3·9 (11·0)	–1·3 (9·1)	–4·2 (8·2)	–4 0 (8·5)	–7·4 (6·6)
I^a	0·2 (8·6)	–0·9 (10·3)	1·8 (9·0)	–1·3 (8·4)	0·3 (8·6)	0·8 (6·3)
II^a	0·4 (8·7)	–0·4 (10·5)	1 8 (9 0)	–1·2 (8 5)	0·3 (8·6)	1·2 (6·3)
III^a	0·5 (9·0)	–1·4 (11·3)	1·7 (9·3)	–0 2 (8·6)	1·5 (8·9)	0·4 (6·3)
IV^a	0·8 (8·9)	–1·0 (10·9)	2·5 (9·4)	–0·1 (8·6)	1·2 (8·9)	0·6 (6 5)
V^a	0·9 (9·0)	–0·1 (11·3)	2·3 (9·4)	–0·3 (8 6)	1·2 (8·9)	0·9 (9 0)
	(*n* = 43)	(*n* = 5)	(*n* = 10)	(*n* = 10)	(*n* = 8)	(*n* = 10)
III^b	–0·1 (8·5)	–3·9 (7·9)	6·9 (7·7)	–0·8 (4·9)	0·0 (9·9)	–4·6 (6·3)
IV^b	–1·3 (7·8)	–2·6 (7·4)	4·7 (7·6)	–3·7 (4 9)	–2·1 (9·8)	–3·8 (5·4)

Table 3. Diagnostic efficacy of abdominal circumference (AC) measurements in detecting fetuses >4000 g (in sample B)

AC (cm)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>34·0	100% (11/11)	78% (25/32)	61% (11/18)	100% (25/25)
>35·0	82% (9/11)	88% (28/32)	69% (9/13)	93% (28/30)
>36·0	73% (8/11)	94% (30/32)	80% (8/10)	91% (30/33)
>37·0	55% (6/11)	100% (32/32)	100% (6/6)	86% (32/37)

Discussion

It was the aim of this study to examine the efficacy of formulas for estimating fetal weight from the AC alone. We thought that the AC was a measurement of higher relevance than fetal weight when diabetic rather than obstetric considerations were made. Furthermore, when macrosomic fetuses are born vaginally it is the shoulder girdle rather than the head that may cause problems. Unfortunately we have no reliable technique for ultrasound determination of the width across the shoulders (Mintz *et al.* 1989), which, however, intuitively should be better predicted from trunk size than from head size. Finally, it is always possible to determine the AC, whereas it may be impossible to measure the BPD accurately if the fetal head is deeply engaged in the pelvis, as was the case in 13 of our 86 fetuses.

The number of comparable studies is small, because most other studies include fetuses of both non-diabetic and diabetic pregnancies, and because we do not routinely measure the femur length. It has been shown, that including the femur diaphysis length in addition to BPD and AC in the models for predicting fetal weight reduces the random error by 15–25% (Hadlock *et al.* 1984). This is apparently also the case in the diabetic pregnancy, though to a lesser extent, standard deviations being reduced by about 10% (Benson *et al.* 1987; Miller *et al.* 1988). However, this improved weight prediction is in a diabetes context less interesting—a fetus that is heavy because of long legs is not necessarily macrosomic.

It is not surprising that the optimized versions (I^a-III^a), as judged from the multiple R^2, had a higher efficacy than the original formulas (I–III) (Table 1), which furthermore were not created specifically for diabetic pregnancies. Formula III^a which is based on AC alone performs slightly poorer than formulas I^a and II^a, which are based on both BPD and AC, but very similar to the simple linear and quadratic functions of AC (formulas IV^a and V^a). All formulas show fairly low random errors of the weight estimates (SD≈8–9%, Table 2), probably in part explained by the absence in this series of very macrosomic (>5000 g) fetuses. Still, if a SD is about 8–9%, and assuming normality, then 10% of weights will be more than 15% in error in either direction.

The Campbell model and the linear model were optimized after inclusion of the 13 data sets in which the BPD was missing (Table 1). These represent fetuses of fairly high birthweight, seven weighed >4000 g, which in part may explain the slightly poorer though almost identical efficacy of these two formulas. Of these two models we have for simplicity chosen the linear one, knowing that the observed linear fit is the result of a non-linear relation being modified by the diabetic condition into a near-linear one.

Up to an AC of 28 cm the weight estimates are about 100 g above those of the original Campbell formula (Campbell & Wilkin 1975). With larger AC values the weight estimates of this customized linear formula are increasingly bigger than those of the original formula (140, 200 and 330 g bigger at 30, 34 and 38 cm AC, respectively), reflecting the fact that a big diabetes baby also will have fat extremities, whereas a big non-diabetes baby is big rather than fat.

Since women with more severe diabetes are less likely to have macrosomic fetuses, we examined the efficacy of the formula in gestational diabetes and in the White (1965) classes B, C, D and F, and found percent deviations of estimated fetal weight of 1·2, 0·8, 3·0, −1·7 and 4·2. Thus the systematic error is independent of the severity of the diabetes, probably because the non-macrosomic, maybe even growth retarded fetus in White classes D and F will have a rather small AC for age, and furthermore will tend to be born earlier. It will usually have an AC below 34 cm, where the deviation between the present formula and the original Campbell formula is fairly small.

The presented formula (IV^b) which is based solely on the fetal AC may therefore be used for estimating fetal weight in diabetic pregnancies, irrespective of the severity of the diabetes. Another illustration of the fairly close correlation between AC and fetal weight is the diagnostic efficacy of AC>36·0 cm in detecting fetuses >4000 g. The observed predictive values of a positive and a negative test of 80% and 93%, respectively (Table 3), are higher than those obtained by others (Benson *et al.* 1987; Miller *et al.* 1988), though not significantly so. One possible explanation could be that these two studies allow for a 7-day interval between ultrasound examination and delivery, whereas the present one accepts only 2 days.

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Received 26 April 1991
Accepted 12 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 479–482

FETAL AND NEONATAL MEDICINE

Lung volume measured by functional residual capacity in infants following first trimester amniocentesis or chorion villus sampling

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ABSTRACT

Objective To determine the incidence of respiratory problems and lung volume abnormalities in babies born after first trimester amniocentesis or chorion villus sampling.

Design A prospective randomized study.

Setting Harris Birthright Research Centre for Fetal Medicine, Paediatric Respiratory Laboratory, King's College Hospital.

Subjects: Babies of mothers who had undergone first trimester amniocentesis ($n = 74$) or chorion villus sampling (CVS) ($n = 86$) for fetal karyotyping because of advanced maternal age, parental anxiety or family history of chromosomal abnormality in the absence of parental chromosome re-arrangement.

Main outcomes Respiratory distress in the neonatal period and lung volume as assessed by measurement of functional residual capacity (FRC).

Results CVS was associated with a significantly higher incidence of neonatal respiratory distress, six infants in the CVS group but none in the amniocentesis group required admission to the special care baby unit because of respiratory distress ($P < 0{\cdot}05$). Although there was no significant difference in the mean FRC between the two groups (amniocentesis 29·7 ml/kg *vs* CVS 29·6 ml/kg) the overall incidence of FRC values <2·5th centile of the normal range was 9%.

Conclusion Both amniocentesis and CVS performed in the first trimester of pregnancy may impair antenatal lung growth.

Amniocentesis in the second trimester has been associated with an increased occurrence of neonatal respiratory problems. The Medical Research Council Working Party (1978) found that neonatal unexplained respiratory difficulties lasting for more than 24 h occurred in 9·2% of infants born at 34–35 weeks gestation and whose mothers had undergone amniocentesis compared with 0·9% of controls. Similarly, Tabor *et al.* (1986), in a prospective randomized study, reported that in the group undergoing amniocentesis at a mean of 16·4 weeks gestation the occurrence of neonatal respiratory distress syndrome and pneumonia was more than doubled compared to the control group. Lung function abnormalities are also increased; Vyas *et al* (1982) examined apparently asymptomatic infants and found that the crying vital capacity in infants whose mothers had undergone amniocentesis was lower than in controls.

Recently, amniocentesis at 10–14 weeks has been introduced as an alternative to chorionic villus sampling (CVS) for first trimester fetal karyotyping. The gestation at sampling and interval between sampling and obtaining a cytogenetic result from cell culture for CVS and amniocentesis are similar (Byrne *et al.* 1991). However, at this early stage in pregnancy, the adverse effect of amniocentesis on lung growth may be even more serious than with second trimester amniocentesis. Extrapolation from data of pregnancies complicated by preterm prelabour rupture of the membranes demonstrates that the earlier the reduction in amniotic fluid volume the worse the effect on lung growth (Blott & Greenough 1988).

We are currently conducting an on-going prospective randomized trial to assess the safety and cytogenetic accuracy of amniocentesis versus CVS at 10–14 weeks gestation and this trial will require 6700 subjects before it is completed (Byrne *et al.* 1991). One aspect of this trial was to examine the possible effect of these techniques on antenatal lung growth by examining the occurrence of neonatal respiratory morbidity and measurement of functional residual capacity (FRC) for assessment of lung volume and therefore antenatal lung growth. Since the smallest different in FRC between the two groups that would have any clinical significance is 1·0 ml/kg, it was aimed to recruit 160 subjects as this would have a 70% power at the 5% level to detect such a difference between the two groups. However, because of concerns regarding the effect of second trimester amniocentesis on lung function (Tabor *et al.* 1986; Vyas *et al.* 1982) an interim analysis of the FRC results was pre-planned after recruitment of 100 babies. At this

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interim analysis there appeared to be no significant difference in the FRC results between the two groups, but the FRC was below the 2·5th centile of our own normal range in a greater proportion of infants (5%) than would have been expected. We now report the occurrence of respiratory problems and lung volume abnormalities in the completed study of the 160 babies.

Subjects and methods

In the CVS *versus* amniocentesis trial the indications for first trimester diagnosis were fetal karyotyping for advanced maternal age, parental anxiety or family history of chromosomal abnormality in the absence of parental chromosomal rearrangement. The exclusion criteria were missed miscarriage, multiple pregnancy, heavy vaginal bleeding at presentation, major fetal abnormalities, multiple fibroids making either procedure impossible, an intrauterine contraception device *in situ* and/or the choice of one procedure because the alternative procedure was considered too difficult. The gestational age at sampling was 10–14 weeks with a minimal fetal crown-rump length of 38 mm. A transabdominal, ultrasound-guided needle (20 gauge) was used for both CVS and amniocentesis; at CVS the amniotic sac was avoided and at amniocentis the placenta was avoided. No local anaesthetic was used for either procedure. At amniocentesis 11 ml of amniotic fluid was removed.

The women with a normal fetal karyotype were requested to have a detailed fetal ultrasound examination at 20 weeks. After this scan, a doctor (P.J.T.), who was unaware of which first trimester procedure had been used asked those women who lived within the district around King's College Hospital whether they would be willing to take part in the present study which would involve examining the postnatal respiratory status of their babies. Of 168 pregnant women approached, four in each group agreed to neonatal follow-up but not to the lung function tests. None of their eight infants had neonatal problems nor did they require admission to the special care baby unit (SCBU). The remaining 160 women agreed to take part in both parts of our study.

All babies were followed from birth and admission and the diagnoses on admission to the SCBU were noted. All diagnoses were made by the clinician in charge who was unaware of the nature of the diagnostic procedure used in the first trimester. Respiratory distress was diagnosed if the baby was tachypnoeic (respiratory rate >60/minute), grunting and had sternal or intercostal recession. Specific respiratory diagnoses were made with regard to the appearance of the chest radiograph, if bacteria were isolated from the baby or if there had been complications at the delivery. Transient tachypnoea was diagnosed if the baby became tachypnoeic with a respiratory rate >60 breaths/min within 6 h of birth but persisting for less than 24 h and if the chest radiograph demonstrated 'wet lungs'. Respiratory distress syndrome was diagnosed if the baby developed respiratory signs which lasted for more than 24 h in association with a chest radiograph demonstrating symmetrically affected opaque fields with a ground glass appearance, the diagnosis was further confirmed by the failure to isolate organisms from either a blood culture or peripheral swabs taken at birth. Pneumonia was diagnosed if the baby had the above abnormal clinical signs with asymmetrical abnormalities on the chest radiograph and organisms were isolated from the endotracheal tube or nasopharyngeal aspirate. Meconium aspiration syndrome was diagnosed if the baby developed signs of respiratory distress and if there had been meconium-stained amniotic fluid at birth and evidence of aspiration at resuscitation.

Babies were recalled for lung function measurements at approximately 4 weeks of life. They were seen in the Paediatric Respiratory Laboratory where their mothers were questioned and the babies were weighed and examined. Lung function was assessed by measurement of functional residual capacity (FRC) using a helium gas dilution technique (Yuksel *et al.* 1991). Measurements were made with the baby in the semi-prone position. The baby breathed through a face mask, held firmly in place to prevent air leaks, into a water-sealed spirometer (Gould Pulmonet III). The accuracy of the spirometer was checked daily with calibrated syringes. The spirometer incorporates a digital display of FRC which was recorded above the respiratory trace at 15 s intervals. When the display remained unchanged for 30 s equilibration was assumed to have occurred and the measurement was discontinued. The traces were coded and analysed blind to the clinical details by A.G. From the trace, the end expiratory level was determined and the FRC calculated. The results were converted to body temperature, pressure saturated conditions and related to the baby's body weight.

To assess the reproducibility of the measurement of FRC in young infants two separate measurements were made in 30 children with a similar postnatal age to the study population. The mean of the differences between the paired measurements was 1·8 ml/kg. The intra-subject reproducibility of the measurement in infants and young children had been calculated previously to be 7·3% The mean FRC of 50 healthy infants (controls) measured in our own laboratory of similar postnatal age to the study population was 30 ml/kg (95% confidence limits ±6 ml/kg).

This study was approved by the King's College Hospital ethics committee.

Trial size

FRC was measured in 30 infants <8 weeks of age, the results were expressed in ml/kg. The standard deviation of these 30 FRC results was 2·6 ml/kg. Thus, recruitment of 160 babies gave us 70% power at the 5% level to detect a difference in FRC between the two groups of 1·0 ml/kg.

Statistical analysis

Differences in the FRC between the amniocentesis and CVS groups were assessed for statistical significance using Student's t-test or the χ^2 test. The confidence intervals were calculated, with the appropriate P-value, from the standard error of the difference between the means of the two groups.

Results

All the pregnant women had the procedure to which they were allocated, but in two women CVS failed to achieve a satisfactory result and therefore they also had second trimester amniocentesis. Both these babies were normal, had no respiratory difficulty and their FRC values were within the normal range; in the comparison between groups the data of these two babies were included in the CVS group. There was no significant difference in the indication for fetal karyotyping, maternal age or parity, mode or gestational age at delivery between the two groups (Table 1). Neither was there a significant difference between the two groups in the postnatal age at follow-up (Table 1).

Ten babies were admitted to the Special Care Baby Unit (SCBU), eight in the CVS group (non-significant). There was no significant difference in the median gestational age between the infants admitted to the SCBU, 40 weeks (range 34–42) and those not admitted 40 weeks (range 35–42). Only two babies were admitted to SCBU from the amniocentesis group; one had congenital septicaemia *(Streptococcus agalactiae)* and the other a congenital cardiac lesion (pulmonary stenosis). Of the eight babies admitted to the SCBU in the CVS group six had respiratory distress, one had bilateral hydronephrosis and jaundice and one had convulsions due to hypoglycaemia. The difference in the number of babies with respiratory distress between the CVS and the amniocentesis group was statistically significant ($P < 0{\cdot}05$). Of the six babies with respiratory distress, specific diagnoses were made in three: transient neonatal tachypnoea, meconium aspiration syndrome and pneumonia *(Enterococcus faecalis)*. The respiratory signs of the remaining three babies settled spontaneously and within 24 h of birth, they were not associated with any abnormalities of chest radiograph appearance. Only two of the six babies required respiratory support. The baby with meconium aspiration syndrome required 5 days of headbox oxygen, maximum concentration 27%, and the baby who developed pneumonia required 2 days of headbox oxygen, maximum concentration 34%. None of the mothers whose infants developed respiratory distress had had chronic leakage of amniotic fluid following the first trimester procedure.

Table 1. Characteristics of the two study groups

Variable	CVS (n = 86)	Amniocentesis (n = 74)
Indication for fetal karyotyping		
Advanced maternal age	77	69
Parental anxiety	9	5
Gestational age at sampling (weeks)	11 (10–14)	11 (10–14)
Maternal age (years)	37 (25-45)	37 (26-44)
Parity	2 (1-5)	2 (1-6)
Gestational age at delivery (weeks)	40 (34-42)	40 (34-42)
Mode of delivery		
Caesarean section		
Emergency	9	9
Elective	4*	3†
Forceps	3	3
Ventouse	0	1
Age at follow-up (weeks)	4 (1-16)	4 (1-16)
Infants admitted to SCBU	8	2
Mean FRC (ml/kg)	29·7	29 6

Results are median (range) values.

* Two for breech presentation and two for previous section.

† Two for breech presentation and one for previous section.

There was no significant difference in the mean FRC between the amniocentesis group (29·7 SD 4·3 ml/kg) and the CVS group (29·6 SD 3·9 ml/kg) (t-test) (Fig. 1). The 95% CI of the difference between the means of the two groups was −1·38 to 1·62 ml/kg. None of the infants was symptomatic at the time of the FRC measurements. Nine babies in the amniocentesis group and 16 in the CVS group had FRC values outside the 95% CI of the reference range (Fig. 1) this difference was not statistically significant (χ^2 test). The six infants with neonatal respiratory distress had significantly higher FRC values (median 34 ml/kg, range 32–40) than the other 154 infants (median 29 ml/kg, range 17–43) ($P < 0{\cdot}03$, Wilcoxon rank sum test).

Discussion

This study has demonstrated that first trimester amniocentesis compared with CVS is not associated with an increase in neonatal respiratory morbidity. Neonatal respiratory morbidity was assessed in two ways: firstly, the need for admission to SCBU because of respiratory distress and, secondly, the occurrence of lung volume abnormalities measured at approximately 4 weeks of age. No excess of infants with neonatal respiratory distress was noted in the amniocentesis group, indeed the reverse trend was found. Interestingly our finding of 7% of babies with unexplained respiratory difficulties after first trimester CVS is similar to the 8·6% reported by the United Kingdom Medical Research Council Study (1978), but in that study this was associated with amniocentesis rather than CVS.

Lung volume was assessed by measurement of FRC, using a helium gas dilution technique. This method of assessment of lung volume may be inaccurate in babies with a high airways resistance, but babies who have impaired antenatal lung growth are more likely to have low rather than high airways resistance (Helms 1982). Furthermore infants with high air-

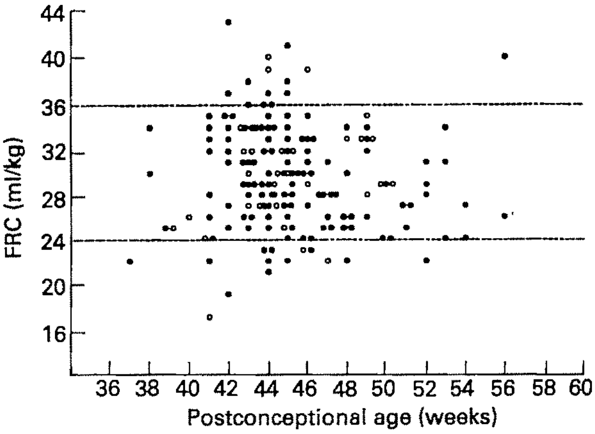

Fig. 1. Functional residual capacity (FRC) in 74 infants born to women who had undergone early amniocentesis (●) and 86 who had chorion villus sampling (○) plotted at the postconceptional age at the time of measurement. The lines indicate the 95% confidence limits of the reference range.

ways resistance, such as children with severe asthma (Greenough *et al.* 1989), who suffer from gas trapping are usually symptomatic (Yuksel & Greenough 1990). Reassuringly none of our population at the time of measurement was symptomatic. Thus, it seems likely that in our study population, measurement of FRC did give an accurate assessment of lung volume and hence antenatal lung growth.

Lung volume may also be measured by plethysmographic estimation of thoracic gas volume (Yuksel *et al.* 1990, 1991). To perform this measurement at 4 weeks of age, the babies must be sedated and we did not feel that it was appropriate to sedate asymptomatic infants solely for the purpose of research lung function measurements. In contrast, sedation is not necessary for measurement of FRC, thus this measurement can be performed throughout the first year of life and facilitate longitudinal determination of the study population's respiratory status. Plethysmographic measurements are time consuming and as a consequence, if we had used this assessment of lung volume, this would have restricted the number of babies who could have been studied. The relatively small, but important, number of babies developing neonatal respiratory distress after second trimester amniocentesis emphasized that we would need a relatively large trial size to avoid a type II error. Thus we felt it appropriate to restrict our assessment of lung volume to measurement of FRC, which we have demonstrated previously to be reproducible and well tolerated in infants (Yuksel *et al.* 1991).

There was a trend towards a greater proportion of babies with abnormal FRC values in the CVS rather than the amniocentesis group, but this was not statistically significant and no statistically significant difference was found in the mean FRC between the two groups. These data suggest that there are no obvious differences between amniocentesis and CVS in the first trimester of pregnancy in their effect on antenatal lung growth. We cannot conclude, however, that these procedures are without effect on lung growth, as the FRC was below the 2·5th centile in four babies in the amniocentesis group and 10 in the CVS group (Fig. 1), which is higher than expected. Amniocentesis in the monkey (*Macaca fascicularis*) resulted in changes in the fetal lungs, which occurred regardless of the amount of fluid removed and even if the membranes were simply punctured and no fluid removed (Hislop *et al.* 1984). The explanation for those findings could be leakage of amniotic fluid continuing for some time after the procedure. Chronic drainage of amniotic fluid following prelabour rupture of the membranes is associated with impairment of antenatal lung growth and the effect is most marked if membrane rupture occurs before 20 weeks gestation (Blott *et al.* 1987; Blott & Greenough 1988).

Some of the babies had an abnormally high FRC and this would not have been expected in babies with impaired antenatal lung growth. The six babies with neonatal respiratory distress had significantly higher FRC values than the rest of the cohort, they represent the major proportion of those whose FRC fell above the reference range. We have demonstrated previously that babies who are born preterm and suffer from neonatal respiratory difficulties tend to have elevated FRC values (Yuksel *et al.* 1991). Although the babies included in the present study were born after 37 weeks gestation, the previous results (Yuksel *et al.*) suggest that neonatal respiratory distress may account for the majority of high FRC values seen in our study population.

This preliminary study suggests that amniocentesis in the first trimester is not associated with a significantly higher risk of impaired fetal lung growth than CVS. We intend, however, to re-assess all the babies at 6 months of age when we hope to confirm that the majority have continuing normal lung growth.

Acknowledgments

We thank Ms Sue Williams for secretarial assistance. Dr P. J. Thompson was supported by the Medical Research Council.

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Received 28 June 1991
Accepted 8 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 483–485

FETAL AND NEONATAL MEDICINE

Fetal middle cerebral artery blood flow during normal active labour and in labour with variable decelerations

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ABSTRACT

Objective To assess the distribution of fetal blood flow impedance of the umbilical and middle cerebral artery in active uncomplicated labour and in labour complicated by variable decelerations.

Interventions Blood flow impedance of the umbilical and fetal middle cerebral arteries was assessed by means of pulsed Doppler ultrasonography and measured by the resistance index (RI) and the systolic/diastolic ratio.

Subjects 35 women at 38-40 weeks gestation admitted to, or monitored in the intrapartum unit. One group of 25 women had a normal active labour, the second group of 10 women were in active labour with moderate variable decelerations. A control group of 25 women—healthy pregnant women at term but not in active labour. All three groups were comparable for maternal age and parity.

Setting Hospital department of obstetrics and gynaecology, Israel.

Design A prospective descriptive study.

Results There was a 40% reduction in middle cerebral artery blood flow impedance in the two groups of women in active labour compared with the control group. Umbilical blood flow did not differ significantly between the three groups. Fetal middle cerebral blood flow impedance in labour was not significantly different in uncomplicated labours and those complicated by fetal heart rate decelerations.

Conclusions During active labour, mechanisms that may be unrelated to low fetal blood oxygen content reduce fetal brain blood vessel impedance.

Fetal cerebral circulation has been investigated recently in normal and complicated pregnancies (Wladimiroff *et al* 1986a, 1986b; Kirkinen *et al.* 1967) using Doppler ultrasonography. Mari *et al.* (1989) described differences in blood flow velocity waveforms in the various vessels of fetal brain. Other studies by Wladimiroff *et al.* (1986b) and Vyas *et al.* (1990a) showed that fetuses with severe intrauterine growth retardation (IUGR) have reduced impedance to blood flow in fetal cerebral arteries.

In the course of normal active labour the placenta has a varying blood supply, although detailed information is lacking. We hypothesized that this may influence the fetal blood flow distribution. We have investigated whether normal active labour following uncomplicated pregnancy is associated with changes in fetal cerebral blood flow impedance; and whether fetal middle cerebral arterial blood flow impedance during active labour differs between fetuses with variable deceleration and those with reactive tracings and no deceleration.

Subjects and methods

The population studied was recruited from women at 38-40 weeks gestation admitted to, or monitored in, the intrapartum unit of Hadassah Mount Scopus University Hospital, between May and September 1990. Pregnancies were uncomplicated by any maternal disease or fetal abnormality. Three groups were studied: groups 1 and 2 included normal healthy women in active labour, who used no drugs or pain relief and all declined epidural anaesthesia. All women meeting these criteria who were in the active phase of first stage labour, between 1000 and 1600 hours when measurements could be performed, were asked consecutively to participate in the study. We excluded women who developed any complication apart from repetitive moderate variable fetal heart rate decelerations. Group 1 included 25 women who had reactive fetal heart rate tracings and no decelerations, 17 of them had ruptured membranes.

The second group comprised 10 women in active labour and with ruptured membranes, who had repetitive moderate variable decelerations for at least 50 min. The decelerations were defined using the criteria of Kubli *et al.* (1969). The suggested cause of variable deceleration in this group was cord compression as no other factors, such as small for gestational age fetuses, pregnancy-induced hypertension, placental abruption, diabetes, etc., were present. The third group constituted the control group and included 25 normal healthy women at term without uterine contractions and with normal non-stress tests. These were referred to the Intrapartum Unit for the purpose of

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Table 1. Clinical characteristics of the three study groups

Variable	Uncomplicated labour ($n = 25$)	Variable decelerations ($n = 10$)	Control group ($n = 25$)
Maternal age	26·1 (3·0)	24·7 (2·1)	25·2 (2·5)
Primigravida (%)	32	30	28
Gestational age (weeks)	39·3 (1·6)	39·0 (1·1)	39·1 (1·1)
Fetal heart rate	139 (28)	145 (38)	147 (31)

All the women had a vaginal delivery.
Results are mean (SD) values.

the study. All three groups were comparable for maternal age and parity.

Fetal umbilical and middle cerebral arterial flow velocity waveforms were obtained transabdominally by one investigator (S.Y.) using duplex phased-wave Doppler ultrasound. Doppler ultrasonogrpahic studies were carried out with an Aloka SSD 650 dynamic image scanner. A 3·5 MHz transducer was used with a 2-3 mm sample volume. The maximal Doppler ultrasonographic energy was 96 mW/cm^2 spatial peak temporal average intensity.

Waveforms were obtained between contractions and after the return of the fetal heart rate (FHR) to baseline to minimize the effect of the FHR on the flow resistance (Brar *et al.* 1989). Measurements were performed only during an active fetal cycle, as judged from the heart rate tracing and fetal breathing movements. Minimal pressure was applied to the maternal abdomen with the transducer to reduce the effect of fetal head compression on the cerebral flow impedance (Vyas *et al.* 1990b). The studies were performed in the absence of gross fetal body or breathing movements (Marsal *et al.* 1984). In four pregnancies belonging to groups 1 and 2 difficulties in obtaining maternal cooperation, mainly due to labour pain, prevented Doppler measurements and four further women were studied. (The date presented in the study refers to the substitute women).

The peak velocity (PV) and the end diastolic velocity (EDV) for each fetus were obtained from three series of flow velocity waveforms, each containing three flow velocity waveforms of satisfactory quality. The mean systolic/diastolic (S/D) ratio and resistance index (RI) values obtained from the three series are given in the text. A digitalized computer system was used to calculate the S/D ratio and the resistance index (RI = PV − EPV/PV).

Table 2. Blood flow velocity waveform indices in the three study groups. Mean systolic/diastolic ratio (S/D) and resistance index (RI) values of fetal middle cerebral and umbilical arteries

Indices	Uncomplicated labour† ($n = 25$)	Variable decelerations† ($n = 10$)	Control group ($n = 25$)
Middle cerebral artery			
S/D	2·12 (0·25)*	2·11 (0·33)*	3·7 (0·45)
RI	0·53 (0.045)*	0·52 (0·09)*	0·73 (0·11)
Umbilical artery			
S/D	2·8 (0·36)	3·1 (0·41)	2·6 (0·31)
RI	0·64 (0·07)	0·68 (0·08)	0·62 (0·05)

*Significantly different compared with the control group, $P<0·01$.
†Measurements were performed during first stage labour at cervical dilatation between 4 and 9 cm
Results are mean (SD) values.

Outcome data were collected for all the pregnancies and included birthweight, presence or absence of meconium, duration of labour, 1 and 5 min Apgar scores, and cord artery blood pH.

Statistical analysis

Student's *t*-test and the χ^2 test were used, as appropriate. A probability value of <0·05 was considered statistically significant.

Results

The mean maternal age, proportion of primigravida, gestational age, and fetal heart rate are shown in Table 1 (for group 2, fetal heart rate was recorded between decelerations). There were no significant differences between the three groups for any of these variables. All the fetuses had cord artery blood pH >7·2. All women had vaginal deliveries.

The mean umbilical artery S/D ratios and RI values were comparable for the three groups (Table 2).

However, the middle cerebral artery S/D ratios and the RI values were about 40% lower in the groups in active labour than the values measured in the control group (women without uterine contractions) ($P<0·01$). There was no difference between the variable deceleration group and the uncomplicated labour group (Table 2). No change in cerebral or umbilical blood flow impedance before, during, or after uterine contractions was detected in the three study groups (data not shown).

The pregnancy outcomes were similar for the three groups (Table 3). There were no significant differences in duration of labour, birthweight, presence of meconium-stained amniotic fluid or low Apgar scores (<7) at 5 min. More babies in the variable deceleration group had low 1 min Apgar scores when compared with the other two groups, but the difference was not statistically significant (Table 3).

Discussion

Fetal hypoxaemia seems to be associated with reduced impe-

Table 3. Pregnancy outcome in the three study groups

Variable	Uncomplicated labour ($n = 25$)	Variable decelerations ($n = 10$)	Control group ($n = 25$)
Duration of labour(h)	9·4 (2·5)	8·5 (2·9)	8·9 (1·6)
Birthweight (g)	3420 (611)	3270 (301)	3334 (517)
Meconium stained amniotic fluid	1	2	2
Low Apgar score (<7)			
At 1 min	1	4	2
At 5 min	0	1	0

Results are mean (SD) values or numbers of women as appropriate.

dance of flow in the middle cerebral artery. This has been shown in grow-retarded fetuses (Wladimiroff *et al.* 1986b; Vyas *et al.* 1990a) and in anaemic fetuses (Vyas *et al.* 1990c). However, the precise relation is not fully understood. On the one hand, Vyas *et al.* (1990a) found a direct correlation between fetal hypoxaemia and the degree of reduction in cerebral flow impedance in growth-retarded fetuses. On the other hand, they concluded that decreased flow resistance in anaemic fetuses was not related to the degree of fetal anaemia, and was not significantly associated with the reduction in PO_2 (Vyas *et al.* 1990c).

In this study we investigated whether active normal labour or labour complicated by variable decelerations was associated with a change in cerebral blood flow in the fetus as reflected by middle cerebral artery flow impedance.

We assumed that in normal active labour there is no fetal hypoxaemia and that when there is mild to moderate variable deceleration fetal hypoxaemia is minimal, if present at all (Kubli *et al.* 1969; Petrie 1986; Abitbol *et al.* 1989).

We found a significant reduction in impedance in the fetal middle cerebral artery during active labour compared with women without uterine contractions. No further decrease in flow impedance was noted when labour was complicated by repeated moderate variable decelerations.

The data presented suggest that relative hypoxaemia may not be the only mechanism involved in the reduction of blood flow resistance in fetal brain. It is tempting to speculate that during active labour a 'protecting' process affects the fetal brain circulation and thus helps to prevent fetal cerebral hypoxia by maintaining stable brain blood flow.

Repeated variable decelerations are commonly associated with reduced feto-placental blood flow (Kubli *et al.* 1969; Petrie 1986; Abitbol *et al.* 1989) and are sometimes associated with mild hypoxaemia. However, in our study of labour the fetuses with variable decelerations had similar middle cerebral blood flow impedance as those with normal fetal heart rate patterns. Further studies are needed to clarify whether severe hypoxaemia during active labour results in a different cerebral vascular response, and to determine the mechanisms involved in cerebral flow regulation during normal active labour.

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Received 14 August 1991
Accepted 12 February 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 486–491

GYNAECOLOGY

Endometrial phospholipases A_2, polycystic ovaries and pelvic pain

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ABSTRACT

Objective To compare the activity of calcium independent phospholipase A_2 in the endometrium of women with polycystic ovaries and in women with normal ovaries, and to investigate the influence of chronic pelvic pain on phospholipase A_2 activity.
Design A prospective descriptive study.
Setting The Samaritan Hospital for Women and the Unit of Metabolic Medicine, St Mary's Hospital Medical School, London.
Subjects 73 women attending the Samaritan Hospital for Women for clip sterilization, infertility, early recurrent miscarriage or pelvic venous congestion. 45 of these women had no pelvic pain, 22 had normal ovaries and 23 had polycystic ovaries diagnosed by ultrasound. The other 28 women had chronic pelvic pain, 14 of them had normal ovaries and 14 polycystic ovaries.
Interventions Endometrial tissue was obtained at curettage or from the excised uterus in the proliferative or secretory phase of the menstrual cycle. The activities of calcium dependent (type 1) and calcium independent (type 2) phospholipase A_2 isoenzymes were measured in all endometrial samples.
Results In all the women phospholipase A_2 type 1 activity, was significantly higher in the secretory phase than in the proliferative phase ($P < 0{\cdot}001$). There was no difference between women with normal ovaries and those with polycystic ovaries at either stage of the cycle irrespective of whether or not chronic pelvic venous congestion was present. In women with normal ovaries, both with and without chronic pelvic pain, phospholipase A_2 type 2 activity was significantly higher in the secretory phase than in the proliferative phase ($P < 0{\cdot}02$ and $P < 0{\cdot}05$ respectively) but in women with polycystic ovaries, with and without chronic pelvic pain, there was no significant differene in activity between the two phases of the cycle. Women with polycystic ovaries had markedly higher proliferative phase type 2 activity than women with normal ovaries ($P < 0{\cdot}001$). Secretory phase type 2 activity was similar in all the women investigated.
Conclusion These data suggest that phospholipase A_2 type 2 activity is increased in proliferative phase endometrium of women with polycystic ovaries but that the increase is not associated with chronic pelvic venous congestion.

Polycystic ovaries are associated with disturbances of reproductive function, notably anovulatory infertility (Adams *et al.* 1986; Hull 1987), early pregnancy loss (Sagle *et al.* 1988) and dysfunctional uterine bleeding (Franks *et al.* 1985). There is also a high prevalence of this ovarian disorder in women suffering from chronic pelvic pain due to pelvic venous congestion (Adams *et al.* 1990).

Women with polycystic ovaries commonly have an enlarged uterus and a thickened endometrium (Adams *et al.* 1988). This morphological abnormality is evident both in women with anovulatory cycles and in those who are ovulating regularly, including women with pelvic venous congestion (Adams *et al.* 1990). In women with anovulatory cycles the cause may be attributed to chronic exposure to unopposed oestrogen but in those who ovulate, the explanation is more elusive. It has become apparent from our recent sudies that polycystic ovaries (as diagnosed by ultrasonography) may be linked with a biochemical abnormality of the endometrium. The role of phospholipases in endometrial function has been the focal point of our investigations. Phospholipase A_2, which cleaves arachidonic acid from the C-2 position of membrane phospholipids, is considered to represent the rate limiting step in the synthesis of prostaglandins of the 2-series, that is prostaglandins E_2 and

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$F_2\alpha$. These prostaglandins play a key role in the regulation of menstrual bleeding, endometrial regeneration and implantation and thus any irregularity in the control of endometrial phospholipase A_2 activity could affect one or more of these important physiological processes. There are two phospholipase A_2 isoenzymes in human endometrium; type 1 is a calcium dependent enzyme which is associated with endometrial glands whereas type 2 is calcium independent and of stromal cell origin (Bonney *et al.* 1987). Our initial findings indicate that the activity of the calcium independent isoenzyme (phospholipase A_2) is significantly increased in the proliferative phase of women with polycystic ovaries compared with women with normal ovaries (Bonney & Franks, 1988; Bonney *et al.* 1990a). The aim of the present study was to confirm and extend these observations and to include in the study of a group of women (with and without polycystic ovaries) suffering from chronic pelvic pain due to pelvic venous congestion.

Subjects and methods

All the women in the study were ovulating (as demonstrated by the presence of a secretory endometrium or an ovulatory serum progesterone value) and had regular cycles. They had no evidence of uterine pathology and had not taken any medication for at least 2 months before curettage. Ovarian morphology was assessed by ultrasonography, supported in most women by laparoscopy or by histology after oophorectomy in women being treated for chronic pelvic pain. Endometrial tissue was obtained, with consent of the woman by either Vabra or Rolon curettage as an outpatient procedure, or by dilation and curettage under general anaesthesia, or from the excised uterus after hysterectomy (pelvic pain patients). A portion of the endometrium was sent to the histopathology laboratory for examination by light microscopy and for endometrial dating and the remainder was stored at −70°C.

Endometrial samples were assigned to the proliferative or secretory phase of the menstrual cycle after the histopathologist's report. The timing of the last menstrual period and serum progesterone values were also taken into account. Sampling was not timed to the stage of the cycle, though this was known at the time of sampling and was used as a guide to enable distribution between the two cycle phases. One sample was obtained from each woman so that samples from proliferative and secretory phases were from different subjects. The study was approved by the local ethics committee of Parkside Health Authority.

Four groups of women were selected for entry to the study:

Women without pelvic pain

There were two groups of women without pelvic pain. One was a control group of 22 women with normal ovaries. This group was selected from women undergoing clip sterilization or from women with infertility due to tubal defects or women who presented with the complaint of menorrhagia but were subsequently found to have a blood loss of less than 40 ml, as measured by the alkaline haematin method of Hallberg & Nillson (1964). Nine women were in the proliferative phase and 13 in the secretory phase of the cycle at time of sampling. The second group comprised 23 women with polycystic ovaries who were identified on the basis of ultrasound appearance of the ovaries. Some women had hirsutism or acne or both, but none had raised serum LH (over 11 *IU/l*) or testosterone (over 3 *IU/l*) values. The women were recruited from patients presenting with infertility or recurrent early miscarriage, seven were in the proliferative phase and 16 in the secretory phase of the cycle at time of sampling.

Women with pelvic pain

The two groups of women with chronic pelvic pain were recruited from patients referred to the pelvic pain clinic at the Samaritan Hospital for Women. The degree of pelvic congestion was assessed by laparoscopy, pelvic venography and ultrasound scanning and a score assigned to indicate the severity of the condition (Beard *et al.* 1984). Only women with a venogram score of > 5 (3 = normal, 9 = severe) and a history of chronic pelvic pain of more than 1 year were included in the study. There was no evidence at laparoscopic or ultrasound examination of any other pathology (e.g., pelvic inflammatory disease, endometriosis, fibroids). Hysterectomy or oophorectomy or both procedures have been shown to relieve chronic pelvic pain and some patients underwent surgery as part of the treatment (Beard *et al.* 1991). Ovarian morphology was assessed by ultrasound, laparoscopy or histology after oophorectomy in some patients. If a clear diagnosis of ovarian morphology was not possible, the woman was not included in the study.

One group of 14 women had normal ovaries, 10 were in the proliferative phase and four in the secretory phase at the time of sampling.

The second group of 14 women had polycystic ovaries. In this group of women ultrasound examination characteristically revealed a spectrum of ovarian abnormality from classic polycystic ovaries where there were 10 or more follicles arranged around a core of stromal tissue, to a pattern characterized by clumps of 4–5 cysts of 5–10 mm in diameter (Adams *et al.* 1990). Nine women were in the proliferative phase and five in the secretory phase at the time of sampling.

Assay of phospholipase A_2 activity

The tissue was homogenized using a polytron homogenizer (Kinematica GmbH, Lucerne, Switzerland) at a concentration of 80–100 mg tissue/ml in 0·25M sucrose and centrifuged at 250 *g* for 5 min. The supernatant fluid was decanted and retained for assay of phospholipase A_2. The protein concentration of the supernatant was measured as described by Lowry *et al.* (1951). No attempt was made to separate glands and stromal tissue before preparing the samples and no assessment of the gland/stroma ratio was made. Phospholipase A_2 activity (types 1 and 2) was measured as described previously (Bonney *et al.* 1987; Bonney & Franks, 1988) using 1-stearoyl 2[^{14}C]-arachidonyl phosphatidylcholine (Amersham International, Bucks, UK) as the substrate. Measurement of type 1 and type 2 activities is based on the calcium and pH requirements of the two isoenzymes. Phospholipase A_2 type 1 has a requirement for calcium and is optimally active in the alkaline pH range (pH 7·5–9·0) whereas type 2 is inhibited by calcium (5 mM calcium is a strong inhibitor) and is optimally active at pH 6·5-7·0 (Bonney *et al.* 1987).

Statistical analysis

As the data were not normally distributed, differences between groups were analysed by the Mann-Whitney *U*-test.

Results

Phospholipase A_2 type 1 activity

The activity of phospholipase A_2 type 1 in proliferative and secretory phase endometrium from women without chronic pelvic pain is presented in Fig. 1 for women with normal ovaries and those with polycystic ovaries. The activity of phospholipase A_2 type 1 was significantly higher in the secretory phase than in the proliferative phase in both groups ($P <$ 0·001), but there were no differences between women with normal ovaries and those with polycystic ovaries, at either stage of the cycle.

The data for the women with the pelvic pain (Fig. 1) show similar profiles for phospholipase A_2 type 1 activity. Enzyme activity was significantly higher in the secretory phase than in the proliferative phase, both in women with normal ovaries ($P <$ 0·005) and in those with polycystic ovaries ($P <$ 0·01). There was no difference between women with normal ovaries and those with polycystic ovaries at either stage of the cycle.

There was also no difference in phospholipase A_2 type 1 activity at either stage of the cycle between women complaining of chronic pelvic pain and those without pain.

Phospholipase A_2 type 2 activity

Figure 2 illustrates the data obtained for phospholipase A_2 type 2 activity in the endometrium of women without chronic pelvic pain. In women with normal ovaries there was a small but significant increase ($P <$ 0·05) in isoenzyme type 2 activity in the secretory phase compared with the proliferative phase. In women with polycystic ovaries, however, there was no significant difference between the two phases of the cycle. Women

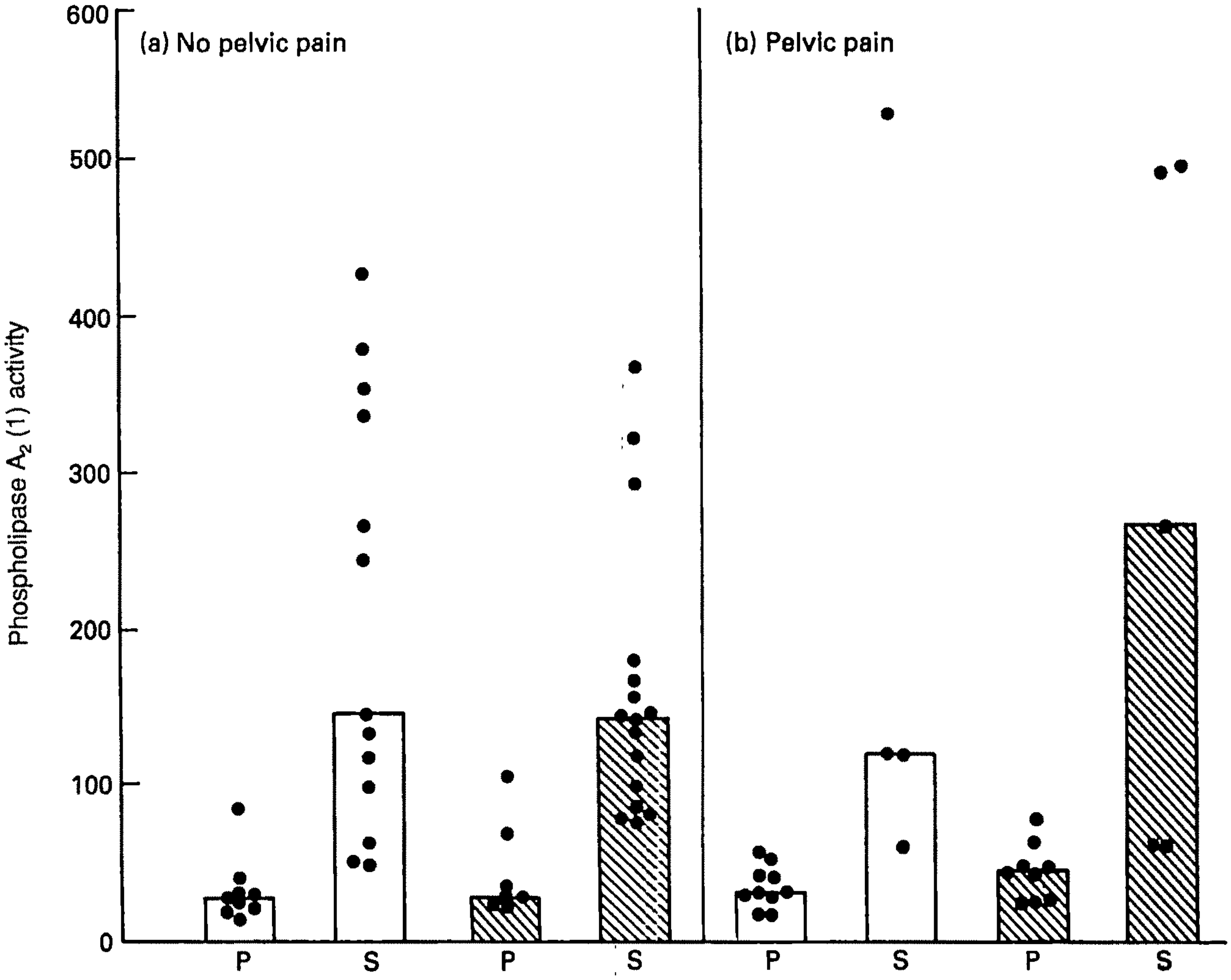

Fig. 1. Phospholipase A_2 type 1 activity (expressed as pmol arachidonic acid released per mg protein per min) in the endometrium of women (a) without chronic pelvic pain and (b) with chronic pelvic pain. Women with normal ovaries (open bars) and those with polycystic ovaries (hatched bars) are subdivided according to the stage of the cycle (P= proliferative phase; S= secretory phase). Each point represents an individual observation and the vertical bars represent the median values. Statistical analysis: Mann Whitney *U*-test. Proliferative *vs* secretory phase for both groups of women without chronic pelvic pain: $P <$ 0·001. Proliferative *vs* secretory phase for women with chronic pelvic pain: normal ovaries $P <$ 0·005, polycystic ovaries $P <$ 0·01.

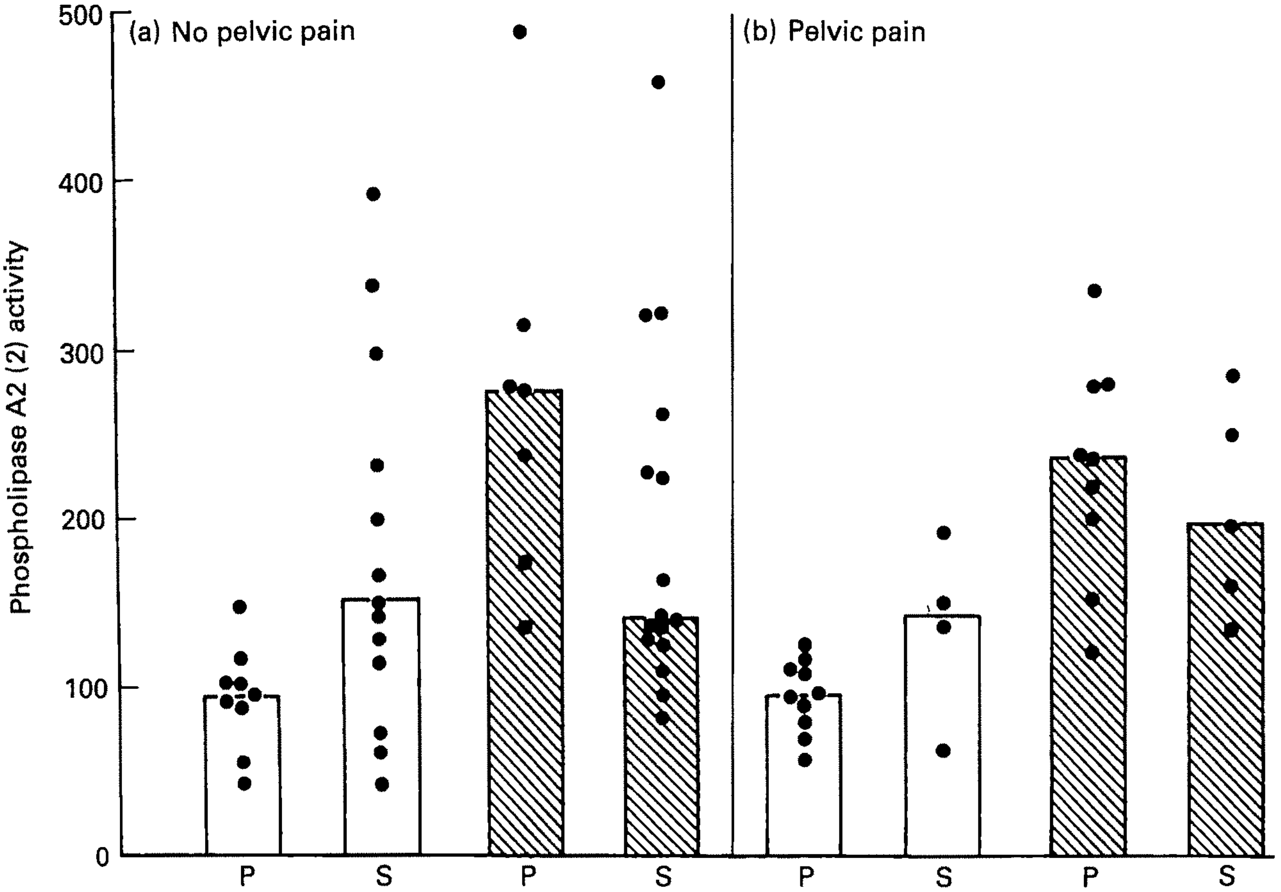

Fig. 2. Phospholipase A_2 type 2 activity (expressed as pmol arachidonic acid released per mg protein per min) in the endometrium of (a) women without chronic pelvic pain and (b) women with chronic pelvic pain For explanation of symbols see Fig 1 Statistical analysis, Mann Whitney *U*-test. For women without chronic pelvic pain: proliferative *vs* secretory phase, normal ovaries $P < 0·05$; polycystic ovaries no significant difference. Normal ovaries *vs* polycystic ovaries· proliferative phase $P < 0·05$, secretory phase no significant difference For women with chronic pelvic pain: proliferative *vs* secretory phase, normal ovaries $P > 0·02$, polycystic ovaries no significant difference. Normal ovaries *vs* polycystic ovaries. proliferative phase $P < 0·05$, secretory phase no significant difference.

with polycystic ovaries were found to have significantly higher phospholipase A_2 type 2 activity in the proliferative phase than women with normal ovaries ($P < 0·001$), with values similar to those in the secretory phase of both groups. There was no significant difference in secretory phase phospholipase A_2 type 2 activity between the two groups.

In women complaining of chronic pelvic pain, the pattern of endometrial phospholipase A_2 type 2 activity was similar to that obtained for women without pelvic pain (Fig. 2). Women with normal ovaries had significantly higher type 2 isoenzyme activity in the proliferative phase than in the secretory phase ($P < 0·02$) whereas in women with polycystic ovaries there was no difference between the two phases of the cycle. Furthermore, as in women without chronic pelvic pain, phospholipase A_2 type 2 activity was significantly higher in the proliferative phase in women with polycystic ovaries than in women with normal ovaries ($P < 0·001$). Secretory phase activity was again not significantly different between women with normal ovaries and those with polycystic ovaries.

These data demonstrate that phospholipase A_2 type 2 activity is significantly higher in proliferative phase endometrium of women with polycystic ovaries than in women with normal ovaries. The presence of pelvic venous congestion was not associated with a change in the activity of either of the phospholipase A_2 isoenzymes. The data for proliferative phase type 2 isoenzyme activity were therefore pooled (women with and without chronic pelvic pain) and grouped according to ovarian morphology. The results are presented in Fig. 3 which illustrates the minimal overlap of phospholipase A_2 type 2 activity between women with normal ovaries and those with polycystic ovaries.

Disscussion

Endometrial phospholipase A_2 type 1 activity, in all groups in the study, was approximately four-fold greater in the secretory phase than in the proliferative phase of the cycle and these cyclical differences were found in the women with and in those without pelvic pain. Similar findings have been reported for normal women (Bonney, 1985; Bonney *et al* 1987) and for those with ovulatory cycles with either menorrhagia (Bonney *et al.*1991) or polycystic ovaries (Bonney & Franks 1990; Bonney *et al.* 1990a). Chronic pelvic congestion was not associated with an increase in phospholipase A_2 type 1 activity at either stage of the cycle. Phospholipase A_2 type 1 is a calcium dependent enzyme which is present in the endometrial glands and its activity may be regulated by ovarian steroids (Bonney

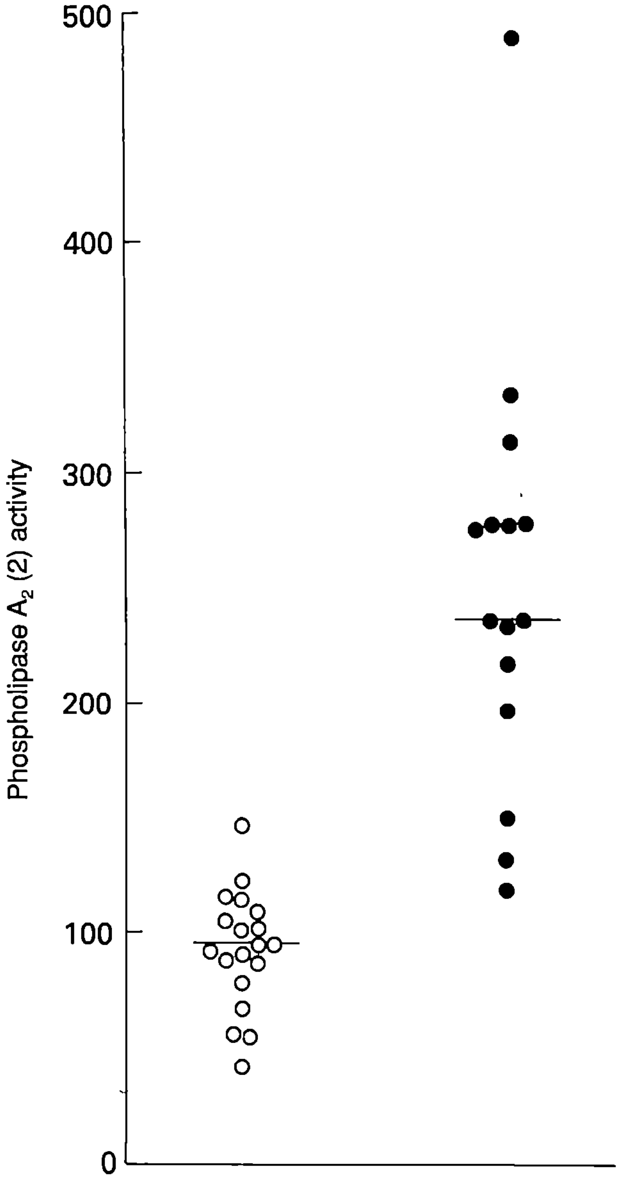

Fig. 3. Phospholipase A_2 type 2 activity (expressed as pmol arachidonic acid released per mg protein per min) in proliferative phase endometrium of women with normal ovaries (open circles) and women with polycystic ovaries (solid circles). The data are pooled from women with and without chronic pelvic pain to demonstrate the minimal degree overlap between the activity measured in the endometrium of women with normal ovaries and those with polycystic ovaries. Each point represents an individual observation (each an average of duplicate estimations) and the median of each group is presented as a horizontal line.

et al. 1987), but the amount of enzyme present will also depend on the growth and development of the endometrial glands during the menstrual cycle. Phospholipase A_2 type 1 activity may, therefore, be viewed as a marker of functional endometrial glands rather than as an indicator of endometrial abnormality.

Phospholipase A_2 type 2 activity is, on the other hand, confined to the stromal component of the endometrium and factors governing the amount of enzyme present may be due to more subtle changes in the tissue such as an alteration in the steroid milieu or in the response of the tissue to steroid hormones or growth promoting factors. Women with normal ovaries, both with and without pelvic pain, showed a small but significant increase in isoenzyme type 2 activity in the secretory phase compared with the proliferative phase. However, in women with polycystic ovaries isoenzyme type 2 activity was markedly higher in the proliferative phase (but not the secretory phase) than in women with normal ovaries. Chronic pelvic congestion had no impact on the activity of isoenzyme type 2 since only women with polycystic ovaries had high proliferative phase isoenzyme type 2 activity. The increased enzyme activity appears to be a manifestation of polycystic ovaries rather than of pelvic congestion. There was little overlap in phospholipase A_2 type 2 activity in proliferative phase endometrium between women with polycystic ovaries and those with normal ovaries, irrespective of the presence of pelvic venous congestion.

The cause of the increased type 2 isoenzyme activity in proliferative phase endometrium of women with polycystic ovaries is not known. These women have a thicker endometrium than those with normal ovaries (Adams *et al.* 1988) and we have suggested that the increased phospholipase A_2 type 2 activity may be a marker of abnormal endometrial growth and function (Bonney *et al.* 1990a). Sagle *et al.* (1988) demonstrated that as many as 82% of spontaneously ovulating women presenting at the recurrent miscarriage clinic had polycystic ovaries. The association implies that a functional abnormality of the endometrium is one possible cause of recurrent miscarriage in women with polycystic ovaries.

The increase in phospholipase A_2 type 2 activity in proliferative phase endometrium of women with polycystic ovaries cannot be due to unopposed oestrogen stimulation, since the women in this study were ovulating and had regular cycles. Serum LH values were also within the normal range. Watson *et al* (1989) measuring daily urinary LH profiles noted abnormally high follicular LH concentrations in 81% of women with a history of early recurrent miscarriage, most of whom had polycystic ovaries. It would appear therefore that a single serum LH measurement fails to detect these subtle changes in LH secretion. However, in women with chronic pelvic congestion, those with polycystic ovaries have been shown to have significantly higher serum LH levels than women with normal ovaries (Farquhar *et al.*, unpublished data).

Another possible explanation for the increase in phospholipase A_2 type 2 activity is an abnormal function of the oestradiol receptor or of one of a number of growth factors and/or their receptors. There is as yet little information concerning the role of growth factors in the development and function of the endometrium but we have recently demonstrated an increase in the proliferation of endometrial cells in culture in reponse to EGF and TGFα and we have shown that the effect of EGF is potentiated by oestradiol (Bonney *et al.* 1990b).

Although the present study demonstrates the potential of the endometrium in women with polycystic ovaries to release a greater than normal amount of arachidonic acid for utilization for prostaglandin synthesis, the extent to which this occurs *in vivo* is not known. An increased sensitivity to oestrogen is likely to affect not only the activity of phospholipase A_2 but also that of cyclooxygenase, thus increasing prostaglandin synthesis. The role of LH in the regulation of endometrial phospholipase activity and prostaglandin synthesis is as yet unknown and will be the focus of our future studies.

Acknowledgments

We gratefully acknowledge the assistance of Professor R.W. Beard and the operating theatre staff of the Samaritan Hospital for Women, London, in supplying the tissue samples used in this study. The work was supported by grants from Birthright, St Mary's Save the Baby Fund and the Wellcome Trust.

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Received 24 June 1991
Accepted 26 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol 99, pp. 492–494

GYNAECOLOGY

Is transcutaneous electrical nerve stimulation of any value during cervical laser treatment?

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ABSTRACT

Objective To assess the value of transcutaneous electrical nerve stimulation (TENS) during cervical laser therapy.

Design Randomized three arm controlled clinical trial comparing (i) TENS, (ii) local anaesthetic and (iii) TENS plus local anaesthetic (direct infiltration of 2% lignocaine and 0·03 iu/ml octopressin).

Setting Colposcopy Unit adapted to run randomized trials.

Subjects 100 women with CIN and no previous experience of cervical surgery.

Main outcome measure Visual linear analogue pain scores.

Results The median pain score associated with TENS was greater than the score associated with local anaesthesia (23% compared with 17%; $P = 0{\cdot}1$). Combining TENS with local anaesthesia did not further reduce pain scores.

Conclusion Although there was considerable consumer satisfaction with TENS it provided no additional pain relieving effect in addition to direct infiltration of lignocaine and it is inferior to lignocaine alone. We are unable to advocate the use of TENS for laser treatment of the cervix.

Cervical laser treatment is an uncomfortable procedure for many women and conventional pain relieving techniques have limitations. Paracervical blocks are ineffective (Johnson *et al.* 1989), non-steroid anti-inflammatory drugs have only a small effect on perceived pain (Al-Kurdi *et al.* 1985) and direct infiltration of local anaesthetic reduces pain scores by 40% (Lee *et al.* 1986). The support of sympathetic nursing staff who are able to distract the patient's attention during the procedure should decrease the amount of discomfort and as a last resort the surgeon may offer selected patients nitrous oxide/oxygen mixture (Entonox) or intravenous fentanyl. Patients who are likely to find laser treatment painful such as young nulliparous women and those who suffer from dysmenorrhoea (Johnson *et al.* 1990) can be offered a general anaesthetic but at present there are no other established techniques that can further reduce the pain associated with cervical laser treatment.

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive method of relieving pain. During the past few years an increasing number of reports have suggested that TENS may give temporary alleviation of pain in about half of those treated. TENS may reduce pain after operations and during parturition but it has not been widely adopted for these purposes because there are many superior analgesics and anaesthetics for these painful conditions. However, the alternatives usually involve the administration of opiates or an epidural block, and are inappropriate for outpatient treatment. Consequently, if TENS could be shown to be effective it could have a place in laser treatment clinics. The analgesic effects of TENS, direct infiltration of lignocaine with octopressin and TENS together with direct infiltration were compared in a three arm randomized clinical trial.

Subjects and methods

The trial protocol was approved by our local ethics committee. One hundred women with a colposcopic diagnosis of cervical intra-epithelial neoplasia (CIN) were recruited. The sample size of 90 was prospectively calculated to detect a 10% improvement in one arm of the study, assuming alpha 0·05, beta 0·2, and the standard errors demonstrated previously (Johnson *et al.* 1989). However, ten more patients were studied than initially intended because we lost count of the number of recruits and failed to stop the trial. The women had had a gynaecological interview, colposcopy and a colposcopically directed biopsy. Linear analogue anxiety and HAD anxiety/depression personality trait scores (Zigmond & Snaith 1983), age and number of vaginal deliveries were recorded to assess group comparability. Women who had a past history of treatment for CIN, other cervical surgery or pelvic inflammatory disease, postmenopausal women and women with cardiac pacemakers were excluded. Two other women refused to enter the trial. All the women were given an explanation of the treatment with reassurance that the treatment would be tolerable.

Suitable subjects were then allocated to one of the following three groups according to a block randomized code. (1) TENS, (2) TENS plus direct infiltration of 2 ml 2% lignocaine plus octopressin 1 in 10 000 (0·03iu/ml); and (3) direct infiltration of 2 ml 2% lignocaine plus octopressin.

As it is impossible to conceal the use of TENS from the

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attendants a sham instrument was not used in group 3. The block randomization code was held by one investigator who then allocated treatment. The nurses, clerical officers responsible for the computerized appointments, and the laser surgeon did not have access to this code. No pre-operative analgesia was offered. Local anaesthesia was administered in a separate room by the investigator responsible for the randomization. A total of 2 ml of 2% lignocaine + octopressin was injected from a dental syringe via a 30 gauge needle into four points on the transformation zone to a depth of 3–5 mm. Microtens TENS pads (Neen Pain Management Systems, Norfolk, UK) were applied 20 min before treatment. Four conductive silicone polymer electrodes were applied using conducting gel and tape fixative; two anteriorly to the abdominal wall just above the symphysis pubis and one on each side of the sacrum. The electrodes were connected to a 80 Hz nerve stimulator (pulse width 210 µs) by a cable. The single channel amplitude control was activated by the patients under instruction. Initially they were encouraged to experience a tingling sensation and then they increased the amplitude until it became uncomfortable. They were given approximately 20 min to experiment with the device until they were called into the second room for laser treatment. All the treatments were carried out in this second room by a second operator who was supported by attentive and sympathetic nursing staff who encouraged the use of TENS. The entire ectocervical transformation zone was either ablated to a depth of approximately 7 mm or excised with the aid of skin hooks using a 35 W CO_2 laser (spot size 1·5 mm). The size of the transformation zone and the amount of blood loss were estimated.

At the end of the procedure the surgeon gave a further explanation of the treatment and scored the pain experienced by the patient using 120 mm visual linear analogue scores (Huskisson 1983). The scores were converted into a percentage. At the end of the procedure the women offered TENS were given a simple questionnaire. They were asked to answer 'Yes' or 'No' to indicate whether or not they found the TENS each of the following: (1) comfortable; (2) unpleasant; (3) helpful (4) frightening; (5) soothing; or (6) pain relieving.

A 'Yes' answer to comforting, helpful, soothing and pain relieving and a 'No' answer to frightening and unpleasant was considered to be a coherent response. If a ratio of favourable to unfavourable responses was at least 3:1 they were considered to be incoherent and the responses were excluded.

The data were analysed according to the 'intention to treat', using the Mann–Whitney U test.

Results

One woman was excluded because she failed to record the pain score. Another found the treatment too uncomfortable and therefore direct local infiltration was added. She had initially scored 37% for the first half of the treatment but found the treatment much more comfortable once local anaesthesia was added.

The median pain score for the group assigned TENS only was higher than the median score for the group given direct infiltration of local anaesthetic ($U = -1{\cdot}57, P = 0{\cdot}116$). Combining TENS with direct local anaesthesia did not further reduce the median pain score. The pain score was unrelated to blood loss, lesion size or whether the lesion was excised rather than ablated (Table 1). The groups had similar anxiety and depression scores.

Fifty-one women who used TENS completed the questionnaire. Six responses were incoherent and nine women claimed the treatment was not painful and they did not need to turn the TENS on. Of the coherent responses 97% found TENS comfortable, 88% thought it was helpful, 75% thought it was pain relieving and 78% found it soothing. However, 10% described it as frightening and 45% said it was unpleasant.

Discussion

Women having laser treatment for CIN find TENS less effective than direct infiltration of local anaesthetic and TENS does not supplement the analgesia of women having local anaesthesia. We had expected TENS to contribute significantly to reducing discomfort during the procedure. The pain of labour is reported to respond to TENS (Augustinsson *et al.* 1977; Tawfik *et al.* 1982; Grim & Morey 1985) but strictly controlled randomized trials have not portrayed TENS so favourably (Simkin 1989) and they have failed to show any difference in measured pain scores (Harrison *et al* 1986; Nesheim 1981).

Table 1. Characteristics of the three groups in the study

Variable	TENS only (n = 34)	Local anaesthetic (n = 35)	TENS and local anaesthetic (n = 29)
Mean age (years) (SD)	31·8 (9)	32·6 (9)	30·1 (8)
% Nulliparae	48%	44%	35%
Lesion			
Small	0	2	1
Average	19	11	7
Large	3	10	3
Excised	12	12	18
Blood loss			
None	25	26	19
Some	6	5	9
Troublesome	3	4	1
Median anxiety HAD score (interquartile range)	6 (5–11)	7 (4–9)	6·5 (4–8)
Median depression HAD score (interquartile range)	3 (1–4)	2 (1–4)	3 (1–3)
Median pain score (interquartile range)	24 (10–42)	17 (7–30)	18 (8–31)

TENS may be effective in relieving chronic and postoperative pain (Sylvester *et al.* 1986; Leo *et al.* 1986; Ho *et al.* 1987; Denning 1988; Anon. 1989) but the pain from laser therapy differs from chronic pain and labour, therefore these reports are not comparable with ours.

Benefit from TENS could be due to a placebo effect and it is only by strictly controlled randomized clinical trials that such an effect can be differentiated from a true effect on pain. The apparent beneficial effect of local anaesthesia must also be considered in the light of the trial's potential weaknesses. It was impossible to conceal the use of TENS from the surgeon and patients but we had intended to 'blind' the attendants to the use of local anaesthesia. Injections of lignocaine were given in a separate room before the laser surgery was carried out by a different attendant but the surgeon was able to identify points where local anaesthetic had been given. The possible influence of recruitment of 10 extra women must also be considered. This occurred because a block of randomly allocated codes was initiated but not completed. Although this would not have affected negative results, it could have influenced the apparent benefit from lignocaine. Block randomization has two advantages: it counteracts temporal bias (due, for example, to improvement in the technique of laser surgery as the study progressed) and it produces equal numbers of subjects in each group. The mismatch caused less women than expected to be recruited into the TENS and local anaesthetic group. If we had become more skilful at laser surgery with the passage of time then this might have improved the median score associated with combination therapy and portrayed it more favourably. Another unexpected outcome, which could have influenced pain scores, was the uneven distribution of large lesions, despite random allocation.

Despite the weaknesses of the trial, which limit conclusions about the effect of lignocaine, there is no evidence that TENS improves pain scores in women having laser treatment of the cervix. The response to the questionnaire could be interpreted very favourably with more than 75% of the women indicating that TENS was pain relieving and 80% of them indicating that it was helpful. We could conclude that it still had a place in our laser clinic because of such favourable responses, even if it has only a placebo effect. However, a substantial proportion of women who used the device found it frightening or unpleasant, which we consider unacceptable in the absence of an improvement in pain scores. Therefore, although we will not object to a motivated woman using her own TENS machine, we are unable to endorse it for routine use for laser treatment of the cervix.

Acknowledgments

We are indebted to Roy Sherlock of Neen Pain Management Systems (Old Pharmacy Yard, Church Street, Dereham, Norfolk NR16 1DJ) for lending us the TENS units and to Professor Richard Lilford and Professor Jim Drife for their help and advice.

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Received 1 March 1991
Accepted 27 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 495–497

GYNAECOLOGY

Detection of hydatidiform mole in maternal serum screening programmes for Down's syndrome

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ABSTRACT

Objective To determine how frequently hydatidiform mole will be detected in a maternal serum Down's syndrome screening programme.

Design Affected pregnancies were identified using a national register. Unconjugated oestriol (uE_3) and human chorionic gonadotrophin (hCG) were measured in stored serum samples and alphafetoprotein (AFP) levels were available from previous neural tube defect screening at 15–20 weeks gestation.

Subjects Ten pregnancies with a complete mole (i.e., hydropic placenta without a fetus), nine with stored serum samples and one with an AFP level only.

Results The median values were 0·08, 0·13 and 1·83 multiples of the normal median for AFP, uE_3 and hCG respectively. Six out of nine (67%) tested for all three markers had a high risk of Down's syndrome given maternal age and the marker levels.

Conclusion Many molar pregnancies that have not presented clinically before 15 weeks will be detected through Down's syndrome screening.

Maternal serum screening for Down's syndrome has become established practice in many centres using alphafetoprotein (AFP), unconjugated oestriol (uE_3) and human chorionic gonadotrophin (hCG). In affected pregnancies AFP and uE_3 levels tend to be low whereas hCG levels tend to be raised and a screening test is regarded as positive if the risk of Down's syndrome given the particular levels and maternal age exceeds a specified cut-off, usually between 1 in 200 and 1 in 400. Like Down's syndrome, hydatidiform mole also occurs more frequently in older women (Bracken 1987) and in most molar pregnancies with a hydropic placenta without a fetus ('complete' mole), AFP and uE_3 levels are expected to be low whilst hCG levels are expected to be high. Therefore in serum screening programs for Down's syndrome some molar pregnancies will be detected after a positive screening test. We investigated this quantitatively using stored serum samples from an antenatal serum bank, and AFP results from a neural tube defect screening program.

Methods and results

A national registration scheme for molar pregnancies has been established since 1973, with cases held on three registers including that in the Department of Medical Oncology, Charing Cross Hospital, London (Bagshawe *et al.* 1986). The identifying details of women on the London register, who were noted to have had their diagnosis made in Oxford, were linked with the list of women who between 1975 and 1983 had serum stored in a –40°C antenatal serum bank as part of a large prospective study, or had maternal serum AFP tests carried out at the John Radcliffe Maternity Hospital, Oxford. The study was restricted to pregnancies between 15 and 20 weeks gestation (based on the interval since the last menstrual period) the time in pregnancy when maternal serum screening for Down's syndrome is performed.

Ten women with a complete mole were identified in this way. In one a serum sample had not been stored so that only an AFP result was available and in one the stored sample had not been tested for AFP. All nine samples were retrieved from storage. AFP was measured in the additional sample by radioimmunoassay (NETRIA); uE_3 and hCG was assayed in all nine samples and in 600 samples from unaffected pregnancies of similar gestational age and duration of sample storage. The person carrying out the assays did not know which samples were from molar pregnancies. uE_3 was measured by radioimmunoassay (Amerlex oestriol RIA Kit) and hCG by an immunoradiometric assay (Serono MAIA-Clone Kit). All results were expressed in multiples of the median (MoM) for unaffected pregnancies of the same gestation derived by regression analysis.

Table 1 shows the individual biochemical results in the 10 complete moles. All the AFP and uE_3 levels were low but not all the hCG levels were high. On average the reductions in AFP and uE_3 levels were greater than the increase in hCG levels (medians of 0·08, 0·13 and 1·83 MoM respectively). Table 1 gives three estimates of Down's syndrome risk, namely those based on maternal age with AFP alone, AFP and hCG and all three markers which are the most common combinations used in practice.

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Table 1. Down's syndrome screening results in pregnancies associated with complete hydatidiform mole

Subject No.	Maternal age at EDD (years)	Gestational age at test (weeks & days)	Marker level (MoM)			Down's risk*		
			AFP	uE_3	hCG	AFP	AFP & hCG	AFP, uE_3 & hCG
1	27	17 + 0	0·35	0·15	1·83	1:310	1:160	>1:51
2	24	18 + 0	0·10	0·38	>11·72	>1:330	>1:18	>1.8
3	24	16 + 3	0·18	0·11	0·60	>1:330	>1:1100	>1:310
4	27	17 + 5	0·06	0·84	1·32	>1:280	>1:270	>1·410
5	37	16 + 4	0·09	0·04	8·73	>1:56	>1:3	>1:1
6	27	17 + 2	0·04	0·10	1·19	>1:280	>1:320	>1:97
7	28	17 + 6	0·23	0·13	3·49	>1:260	>1:35	>1:13
8	28	16 + 4	0·05	0·10	0·37	>1:260	>1:1600	>1:450
9	25	18 + 1	0·07	1·09	8·59	>1.310	>1.18	>1:43
10	28	17 + 3	0·06	—	—	>1:260	—	—

Abbreviations: EDD, estimated date of delivery; MoM, multiple of the median for unaffected pregnancies of the same gestational age; AFP, alphafetoprotein; uE_3, unconjugated oestriol; hCG, human chorionic gonadotrophin.

*Based on age and marker level, as described by Wald *et al.* (1992). Risk cannot be precisely estimated in women with levels outside the range 0·33–3·0 MoM for AFP, 0·40–2·5 MoM for uE_3 and 0·20–5·0 for hCG; it is taken to be < or > that for the nearest value in range, as appropriate.

Using maternal age and AFP alone only one subject (No. 5) had a risk high enough to be unequivocally positive: the remainder had risks close to the cut-off value normally adopted in Down's syndrome screening (1 in 200–1 in 400). Using hCG, as well as AFP, a further four pregnancies were unequivocally positive (nos 1, 2, 7 and 9). Using all the markers together an additional pregnancy (no. 6) was positive, yielding a detection rate of 67% (6/9).

Three partial moles (i.e., hydropic placenta, with a fetus) were also identified. Samples from these pregnancies were not measured for levels of uE_3 and hCG because partial moles were not expected to be detected by Down's syndrome screening. However, it is noteworthy that all would have been detected by neural tube defect screening: one had spina bifida and an AFP level of 15 MoM; the two others ended in intrauterine death and the AFP levels were 17 and 13 MoM.

Discussion

We estimate that many complete moles that did not present clinically early in pregnancy would be detected through Down's syndrome screening at 15–20 weeks gestation. The prevalence of hydatidiform mole is about 1–2 per 1000 pregnancies in this country and about two-thirds are complete moles (Bagshawe *et al.* 1986). The prevalence at 15–20 weeks gestation will be much less, so that if the Down's screening test is positive there will be a much greater likelihood that the pregnancy is affected by Down's syndrome than mole.

Maternal serum AFP and uE_3 concentrations increase in the second trimester as a result of fetal liver production of AFP and fetal adrenal production of oestrogen precursors and metabolism in the fetal liver. The finding of low AFP levels in complete molar pregnancies is therefore expected and confirms the results of other studies of a similar size (Seppälä *et al.* 1972); Ishiguro 1975). We know of only one other publication reporting uE_3 levels in molar pregnancies; this included one pregnant with a value of <0·10 MoM (Tulchinsky & Abraham 1971). Maternal serum hCG is a placental product so that levels might be expected to be altered in the presence of an abnormal placenta. In our series there were some extremely high levels and some relatively low. In two previous series, although cases were not compared with gestation matched controls, it appears that hCG levels were very high in all eight cases from one series (Dawood *et al.* 1977; gestational age 12–20 weeks) and at least six out of seven cases from the other (Ozturk *et al.* 1988; 10–15 weeks). In a further series of seven cases with comparable controls, all were high (Crosignani *et al.* 1974; 10–24 weeks).

A complete mole is more likely than a partial mole to lead to malignancy, although the prognosis with either is likely to be good with efficient treatment and follow-up. The principal benefit of detection through Down's syndrome screening will not be any material improvement in prognosis, but rather the earlier identification of a non-viable and potentially dangerous pregnancy.

Acknowledgments

We thank Professor Bagshawe for supplying us with lists of molar pregnancies in the national registration scheme, and Nora Jones for help in the identification of cases.

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Received 14 August 1991
Accepted 16 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 498–502

GYNAECOLOGY

The cytological detection of persistent cervical intraepithelial neoplasia after local ablative treatment: a comparison of sampling devices

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ABSTRACT

Objective To determine whether the cytological detection of persistent cervical intraepithelial neoplasia (CIN) after local ablative treatment is improved by the use of sampling devices other than the Ayre's spatula.

Design A randomized controlled study.

Setting Lothian Area Colposcopy Clinic.

Subjects 856 patients who had received local therapy (CO_2 laser or cold coagulation) for CIN II or III between 9 and 30 months earlier.

Intervention Each patient had three consecutive cervical smears taken, one with the Ayre's spatula, one with either the Aylesbury, the Rocket or the Multispatula device, and finally one with the Cytobrush. The allocation of which spatula and the order of the first two was randomized. Each patient had a colposcopic examination immediately after the smears were taken.

Main outcome measures A comparison of the detection of histologically proven persistent CIN by the Ayre's spatula with the detection of persistent disease by alternative sampling devices.

Results Of the 856 patients 130 had histologically proven persistent CIN. Another 98 had suspicious findings on colposcopy but punch biopsies reported as histologically normal. Of the remaining patients with normal colposcopy 130 were randomly selected to form a control group. The cervical smears from these 358 women were reported. Significantly fewer Ayre's samples contained endocervical cells than Aylesbury samples (47% *vs* 59%, difference 12%; 95% CI 3%–21%; $P<0{\cdot}001$), Rocket samples (47% *vs* 67%; difference 20%, 95% CI; 12%–32%; $P<0{\cdot}001$) or Multispatula samples (47% *vs* 76%; difference 29%, 95% CI 19–38%; $P<0{\cdot}001$). When punch biopsies contained CIN, dyskaryotic cells were seen in 10% of Ayre's samples, 4·3% of Aylesbury samples, 8·3% of Rocket samples, and in no smear taken with the Multispatula. Obtaining a third smear with the Cytobrush did not substantially improve the detection rate of dyskaryosis. Neither the order of use of the spatulas, the form of initial treatment nor the size of the transformation zone had any apparent effect on the cytological detection of persistent CIN.

Conclusions We recommend that surveillance of patients who have received local ablative therapy for CIN should be by both cytology and colposcopy, and that cytological samples should be obtained using the Ayre's spatula.

In Lothian, as elsewhere in the United Kingdom, the number of women with abnormal cervical cytology being referred for colposcopy has increased exponentially over the last 10 years causing a considerable increase in workload. In 1978 a total of 98 patients was referred to the Lothian Area colposcopy clinic and in 1988 the number of new patients referred was 2313, with a total number of 9839 patients being seen at the clinic in that year. It is our practice to review patients who have received local ablative treatment for cervical intraepithelial neoplasia (CIN) by cervical cytology at 6, 12 and 24 months with the addition of colposcopic examination at 12 months after treatment. Work has been published from other centres (Lopes *et al.* 1990) suggesting that patients can be followed up safely after treatment by using cytology alone, thus reducing the workload of colposcopy clinics. We have been reluctant to adopt this approach because of the well recognized phenomenon of false negative cervical cytology (Shield *et al.* 1987). The false negative rate using the conventional Ayre's spatula for routine

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screening is reported to be between 2% and 40% (Hudson 1985; Morell *et al.* 1982; Giles *et al.* 1988) and the technique has been found to be even less reliable after treatment of CIN (Smart *et al.* 1986; Maclean *et al* 1987; Brunskill *et al.* 1988). There are reports that substituting the Aylesbury spatula (Wolfendale *et al.* 1987), the Multispatula (Vierhout 1987) or the Cytobrush (Boon *et al.* 1986) for the Ayre's spatula may improve the detection rate of CIN. The present study was designed to compare the Aylesbury spatula, the Multispatula, the Rocket spatula and the Cytobrush with the Ayre's spatula for screening for persistent CIN after local ablative treatment, to determine whether cytological detection of persistent disease could be improved sufficiently to allow discontinuation of routine colposcopic review. Table 1 shows the relative cost to the health service of the devices compared.

Patients and methods

A total of 856 patients was entered into the trial. These patients had received CO_2 laser or cold coagulator treatment to the cervix for histologically proven CIN grades II or III between 9 and 30 months earlier. In no patient had there been any suspicion of invasive disease at the time of treatment. The upper limit of the cervical transformation zone had been clearly visible at the time of treatment and the abnormal epithelium was confined to the cervix and did not extend on to the vagina. Patients had been randomly allocated to receive CO_2 laser or cold coagulator treatment as part of a previous study (Smart *et al.* 1986). All patients had had a cervical smear taken which had been reported normal approximately 6 months after treatment. Patients gave informed consent to participating in the present study, and pregnant patients were excluded. The study received the approval of the local ethics committee.

Cervical cytology and colposcopy

All patients had three cervical smears taken under colposcopic control. All had smears taken with both the Ayre's spatula and Cytobrush. In addition, each patient was randomly allocated, using a computer generated technique, to have a smear taken with either the Aylesbury, the Rocket or the Multispatula. Each patient's allocation of spatula, and order of use of spatulas, was contained in a sealed envelope which was only opened on entry into the trial. Thus the Ayre's was used either first or second and the 'test' spatula (Aylesbury, Rocket or Multispatula) correspondingly second or first. The Cytobrush was always the third sampling device to be employed. The sample obtained with each device was spread on a separate glass slide and fixed immediately in methylated spirit (74 OP). Colposcopic examination was then performed routinely by a member of the colposcopy clinic medical staff. A 3% solution of acetic acid was applied to the ectocervix, followed by Lugol's iodine. The colposcopist recorded the size of the cervical transformation zone, whether the upper limit of the transformation zone was visible and whether any colposcopic abnormality was seen. Punch biopsies were taken from any suspect area and fixed immediately in Bouin's solution to be processed routinely for histological examination.

Table 1. Relative costs of five spatulas used for cervical screening

Spatula	Cost per spatula
Ayre's	1·8p (inc. VAT and p+p)
Aylesbury	2 0p (inc. VAT and p+p)
Rocket	7·5p (exc p+p)
Multispatula	27·6p (exc. VAT and p+p)
Cytobrush	13·2p–17·1p (exc. VAT and p+p)

Prices supplied by Manufacturers at December 1990.

Of the 856 patients studied, 130 (15·2%) were found to have histologically proven CIN. All three slides from each of these 130 patients were read, as well as all slides from 98 patients who had had histologically normal cervical target biopsies taken from a colposcopically suspect area. In addition all three slides from each of 130 randomly selected patients with normal colposcopy were reported on. The random selection was computer generated.

All cytology slides were read 'blind', i.e., the two participating screening technicians were not told which device had been used to obtain each sample, which samples had come from the same patient, or whether or not the patient had histologically proven residual CIN. The screeners reported upon the number of squamous and endocervical cells present (scoring on a categorized scale of 0–5, where 0=none, 1=very few, 2=few, 3=moderate, 4=many, 5=abundant), the amount of blood present and the presence or absence of dyskaryotic cells.

Statistical methods

Methods for analysis of cross-over trials (Armitage & Hills 1982) were used to compare the Ayre's with the Aylesbury, Rocket and Multispatula devices. Each of the three test spatulas was compared separately with the Ayre's in the following way. To avoid possible problems with the first sample being systematically different from the second sample, the score of the second spatula was subtracted from the score of the first spatula. These differences were then compared between the group of patients in whom the Ayre's spatula had been used first and the group of patients in whom the 'test' spatula had been used first using a Wilcoxon rank sum test. In the absence of a spatula effect, these two groups should give similar results, but if the spatulas have different effects this should be reflected in the comparison being made.

Confidence intervals for the difference in proportions were calculated using a normal approximation to the standard error of the difference between correlated proportions (Gardner & Altman 1989). This method does not allow for the order effect present in the data, and will result in confidence intervals which are slightly wider than they would be if the order effect was taken into account.

Results

Squamous cells

The Ayre's spatula obtained more squamous cells than any of the other three spatulas. The crude percentages of samples scoring 4 or 5 for squamous cells on the categorized scale were Ayre's 67%, Aylesbury 47% ($P<0{\cdot}01$), Rocket 58% ($P>0{\cdot}05$) and Multispatula 53% ($P<0{\cdot}05$). The P values were calculated after comparing the Ayre's spatula with each of the 'test' spatulas. Fewer squamous cells were sampled by the second spatula, 63% of spatulas used first obtained squamous cell scores of 4 or 5 whilst 56% of spatulas used second obtained equivalent numbers of squamous cells.

Endocervical cells

Each of the 'test' spatulas (the Aylesbury, the Rocket and the Multispatulae) was more efficient at obtaining endocervical cells than the Ayre's spatula. The percentages of samples taken with each spatula containing endocervical cells are shown in Table 2. In addition the second sample contained more endocervical cells than the first sample, the crude percentages of samples containing any endocervical cells being 52% (first spatula used) and 62% (second spatula used) ($P<0{\cdot}01$).

Bleeding

Significantly more blood was noted in the samples taken with the second spatula (34% contained blood) when compared with samples taken with the first spatula (13% contained blood) ($P<0{\cdot}001$).

Dyskaryotic cells

The results concerning the detection of dyskaryosis by each spatula are given in Table 3. It can be seen that no test spatula was significantly better than the Ayre's spatula at detecting dyskaryosis. The first spatula used for each patient was not significantly better or worse than the second one at detecting dyskaryosis. In Table 3 the results obtained by combining the Cytobrush with each spatula are also displayed. Again no one spatula and brush combination was demonstrably better than any other spatula and brush combination. Addition of the Cytobrush did not substantially improve the detection rate of dyskaryosis.

Relation between grade of persistent CIN and cytological detection of dyskaryosis

The efficiency of cytology in the detection of persistent CIN in patients with CIN I, II and III is displayed in Table 4. Patients are included in the 'dyskaryotic' group if any of their three cervical smears (i.e., samples taken with the Cytobrush, the Ayre's or the 'test' spatula) contained dyskaryotic cells. It can be seen from Table 4 that cytology was better at detecting residual CIN III (4 of 10 cases detected) or CIN II (5 of 30 cases detected) than CIN I (8 of 90 cases detected).

Table 2. Cytological detection of endocervical cells

	Number (%) of samples containing endocervical cells	Difference between detection of endocervical cells by the Ayre's spatula, and by other spatulas (95% CI)
Ayre's (n=358)	168 (47)	
Aylesbury (n=116)	68 (59)	12% (3–21)*
Rocket (n=120)	81 (67)	20% (12–32)*
Multispatula (n=129)	98 (76)	29% (19–38)*

n=number of patients.

*$P<0{\cdot}001$, calculated after comparison with Ayre's spatula.

Relation between treatment and cytological detection of dyskaryosis

There was no demonstrable difference between the cytological detection of persistent CIN in patients who had been treated with the CO_2 laser and those who had been treated with the cold coagulator.

Relation between extent of transformation zone and cytological detection of dyskaryosis

In the 99 patients with histologically proven CIN for whom the extent of the transformation zone was adequately recorded, 87% of transformation zones were described as occupying less than 25% of the ectocervix, 11% as occupying 25–50%, and 2% as occupying more than 50% of the ectocervix. Dyskaryotic cells were identified in cervical smears from 13 of these 99 patients. There were dyskaryotic cells in the smears from 10 of the 86 (12%) patients with transformation zones occupying less than 25% of the ectocervix, in 3 of 11 (27%) with 25–50% of the ectocervix occupied and in neither of the patients with a larger transformation zone.

Patients with dyskaryotic smears and with no colposcopic abnormality

There were six patients in this category (see Table 4). One of these patients was found at repeat colposcopic examination to have CIN II. One patient has moved out of our area and is being followed up elsewhere. The other four patients are still under review. No colposcopic abnormality has been detected and their cervical cytology has reverted to normal.

Patients with dyskaryotic smears and with histologically normal colposcopic biopsies

There were six patients in this category (see Table 4). One of these patients has subsequently undergone total abdominal hysterectomy for menorrhagia. No pelvic abnormality was

Table 3. Cytological detection of cervical intraepithelial neoplasia (CIN) by different spatulas in patients with histologically proven CIN

	Spatula alone n (%)	Spatula + Cytobrush n (%)
Ayre's (n=130)	13 (10)	16 (12)
Aylesbury (n=46)	2 (4)	3 (6)
Rocket (n=48)	4 (8)	6 (12)
Multispatula (n=36)	0	2 (6)

n=number of dyskaryotic smears.

Table 4. Cytological detection of cervical intraepithelial neoplasia (CIN)

	Normal colposcopy (n=628)	Suspicious colposcopy (n=228)			
		Biopsy histologically normal	CIN I	CIN II	CIN III
Number of patients sampled	130	98	90	30	10
Number with dyskaryotic smears (%)	6 (4·6)	6 (6·1)	8 (8·9)	5 (16 7)	4 (40·0)

detected and histological examination of the cervix revealed no evidence of CIN. One patient underwent diathermy loop excision of the cervical transformation zone. No histological abnormality was detected. One patient was found to have evidence of papillomavirus infection without CIN on cervical biopsy. The other three patients in this group are still under review. No significant abnormality has been detected on histological examination of cervical biopsies and their cervical cytology has reverted to normal.

Discussion

The Ayre's spatula has been widely criticized on the grounds that it is insufficiently sensitive in the detection of CIN (Wolfendale *et al.* 1987; Vierhout 1987; Brunskill *et al* 1988). It is not possible to draw any conclusions from our data with regard to screening or detection of CIN *de novo* as our findings relate solely to the situation following treatment. We have shown, however, that other cytological sampling devices do not improve the detection rate of persistent CIN after local ablative treatment. Cytology, using any device, picked up only 17 of the 130 histologically proven CIN (or an 87% failure rate). Admittedly 90 of these 130 were merely reported as CIN I, a diagnosis open to considerable reporter variation (Robertson *et al.* 1989), but cytology also failed to diagnose 31 of 40 with CIN II and III (or 77%).

The Ayre's spatula was more efficient at sampling squamous cells than the other devices tested although, in relation to the Rocket spatula, this difference was not statistically significant. The other spatulas tested were significantly more efficient at obtaining endocervical cells than the Ayre's spatula, but this difference was not reflected by an improvement in the detection of dyskaryosis. It has been widely postulated that there is a strong correlation between the presence of endocervical cells and the detection of dyskaryosis (Elias *et al.* 1983). It is interesting, however, that in a recent study of women attending a colposcopy clinic (Woodman *et al.* 1991) smears taken with the Rocket spatula were significantly more likely to contain endocervical cells than smears taken with the Ayre's spatula, but were no more likely to contain dyskaryotic cells. This mirrors the results reported here.

It was thought that perhaps the Ayre's spatula failed to detect areas of persistent CIN because the abnormal epithelium was hidden within the endocervical canal. The Cytobrush was therefore used for each patient, in addition to the other sampling devices, to determine whether this would improve the detection of CIN by better sampling of the canal. The detection rate of CIN by this method was only 12% at best (when the Rocket spatula was used in combination with the Cytobrush—see Table 3) which is still unacceptably low.

It is noteworthy that although there was a strong relation between grade of persistent CIN and cytological detection of CIN (Table 4), the size of the transformation zone after treatment bore no significant relation to the cytological detection of persistent CIN. However, most of the transformation zones and residual lesions observed in our study were small so that we cannot draw any firm conclusions from these data.

It is also interesting that the form of treatment used initially (CO_2 laser ablation or cold coagulator) had no apparent influence on the subsequent cytological detection of persistent CIN. The cold coagulator is cheaper and permits more rapid treatment than the CO_2 laser and has been shown to be equally effective (Smart *et al.* 1986). It is reassuring therefore to find that these advantages are not offset by an increased negative cervical smear rate.

The practice of performing colposcopy to review patients with treated CIN has been criticized on the grounds that colposcopy in these patients has a very high false positive rate (Lopes *et al* 1990) resulting in unnecessary cervical biopsies with attendant morbidity. Whilst conceding that suspicious colposcopy can not infrequently be due to the presence of immature squamous metaplasia, we do not consider this to be a significant problem when follow up colposcopy is delayed until one year after treatment. The false positive rate for colposcopy in our study was 98 of 228 (43%) (Table 4), compared with 91% at 6 months reported by Lopes *et al.* (1990), and we believe that the morbidity associated with punch biopsy or diathermy loop excision is extremely small.

Patients with previously treated CIN are an 'at risk' group for CIN (either persistent or recurrent) and for invasive cervical carcinoma (Intercollegiate Working Party on Cervical Cytology Screening 1987). Our experience has demonstrated the importance of employing both colposcopy and cytology in the initial follow up of these patients and we have found no evidence that the more expensive and sophisticated devices studied are any better at detecting residual CIN than the standard Ayre's spatula.

Acknowledgments

This work was supported by a grant from the Royal Infirmary of Edinburgh Cancer Research Fund. We are very grateful to the staff of the Lothian Area Colposcopy Clinic for their help, and to Carole Cowan and Anne Stevenson for expert cytological technical assistance.

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Received 30 May 1991
Accepted 19 November 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 503–507

REPRODUCTIVE SCIENCE

Erythrocyte membrane composition in pregnancy-induced hypertension: evidence for an altered lipid profile

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ABSTRACT

Objective To investigate whether the increased membrane fluidity postulated as a possible contributing factor to the hypertensive states of pregnancy is related to the lipid composition of the erythrocyte membrane.

Design An observational case control study.

Subjects 30 women with pregnancy induced hypertension, 26 normotensive pregnant women matched for gestational age, and 10 normotensive non pregnant nulliparous women.

Interventions Erythrocyte membranes were prepared from venous blood samples obtained from all the women.

Main outcomes measures Lipid analysis, including cholesterol to phospholipids ratio, distribution of phospholipid classes and fatty acid composition of total phospholipids in erythrocyte ghosts.

Results The cholesterol/phospholipid ratio was significantly higher in the women with pregnancy induced hypertension compared with the normotensive pregnant women (mean 1·24, SD 0·31, 95% CI 1·12 to 1·35 *vs* mean 0·90, SD 0·09, 95% CI 0·86 to 0·94; $P < 0{\cdot}01$). Normotensive non-pregnant erythrocyte membrane cholesterol/phospholipid ratio was 0·88 (SD 0·11, 95% CI 0·79 to 0·96). The percentage distribution of different phospholipid classes and fatty acid composition was similar in all the four groups.

Conclusions The increased cholesterol/phospholipid ratio of the erythrocyte membrane found in pregnancy-induced hypertension represents one factor involved in the pathophysiology of this condition and a possible biochemical marker of the disease.

Among the functional abnormalities associated with pregnancy-induced hypertension are alterations in haemorheological factors, in particular a reduced plasma volume and a concomitant increase in blood viscosity (Buchan 1980). Blood viscosity is determined by the chemical and physical properties of corpuscles and plasma components, and is the principal limiting factor on flow in the microcirculation, particularly in the placental microvessels (Gaehtgens 1980). The density of red and white cells and their deformability are important in determining blood viscosity (Murray *et al.* 1968).

The determinants of red blood cells deformability are mainly the ratio between area and volume, the 'internal viscosity', that is the density of haemoglobin packing within the cell, and the membrane properties. Alteration in any of these factors *in vitro* and *in vivo*, as in hypoxia (Hakim *et al.* 1988) and acidaemia (Norton *et al.* 1981), have been shown to be responsible for reduction in erythrocyte deformability.

The fluid-lipid bilayer of the cell membrane influences the movements of protein molecules. Some membrane proteins act as receptors or are responsible for transport or enzymatic processes; any change of membrane fluidity may compromise their metabolic functions. Cholesterol is an important component of cell membranes, maintaining the bilayer matrix in a fluid state. However, any abnormal increase of membrane cholesterol with respect to total phospholipids leads to impairment of the fluidity of biological membranes and to a decrease in cell deformability (Cooper *et al.* 1978). The phospholipid composition of the cell membrane also plays a key role in the maintenance of membrane fluidity.

Little data are available on the lipid composition of erythrocyte membranes in pregnancy induced hypertension. In the present study we analysed the composition of membrane lipids of erythrocytes in this condition. Lipid composition was studied because the fluidity and the deformability depend mainly on membrane lipid composition (cholesterol/phospholid ratio, phospholipid fatty acid profile) which determines many physiological and biochemical properties of the erythrocyte membrane.

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Subjects and methods

The study included 30 primigravidae with pregnancy-induced hypertension (PIH), 10 of these women also had proteinuria (>0·4 g urinary protein/24 h), 26 normotensive primigravidae with uncomplicated pregnancy and 10 non-pregnant nulliparous women. The normotensive pregnant women were chosen from those attending the prenatal clinic and were matched for maternal and gestational age; women who had a family history of hypertension were excluded. No drugs other than iron supplementation were taken by the pregnant women. The women with pregnancy-induced hypertension had blood pressures of ≥140/90 mm Hg measured on at least two occasions 24 h apart (Davey *et al.* 1986). The women in the control group were recruited from nulliparous members of staff who had blood pressures <135/80 mm Hg. None of the subjects included in study had a family history of hypertension. The clinical details are summarized in Table 1.

Preparation of erythrocyte membranes

A 10 ml sample of venous blood was obtained by venipuncture from the antecubital vein and mixed with heparin at a final concentration of 15 IU/ml. The erythrocytes were sedimented by centrifugation at 300 *g* and washed three times with isotonic phosphate-buffered saline (pH 7·4) at 4°C. Haemoglobin-free membranes were prepared (Dodge *et al.* 1962), using hypotonic phosphate buffer.

Lipid analysis

Lipids were extracted from the erythrocyte membranes (Folch *et al.* 1957). The protein content was estimated in the non-extractable residue as described by Lowry (*et al.* 1951) using bovine serum albumin as standard. Aliquots of the extracted lipids were used to estimate cholesterol and total phospholipid.

The cholesterol content of the erythrocyte membrane was estimated using a modified colorimetric method (Rudel *et al.* 1973). Briefly, 2 ml of *o*-phthalaldehyde (0·05% in acetic acid, w/vol) were added to 100 μl of the lipid extract in chloroform/methanol (2:1) and mixed after 10 min to 1 ml of sulphuric acid. The resulting colour was read at 550 nm within 10–20 min of the addition of sulphuric acid. Cholesterol content was normalized to protein content of the membrane preparation and expressed as μmol/mg protein.

The amount of phospholipid was determined as inorganic phosphorus after digestion of the phospholipids in perchloric acid (Bartlett 1958) and expressed as μmol/mg protein. The cholesterol/phospholipid molar ratio was expressed as moles of cholesterol/moles of phospholipids (Owen *et al.* 1982).

Phospholipid classes were separated on silica gel plates using two-dimensional thin layer chromatography, with chloroform/methanol/aqueous ammonia (65:25:4) as the first solvent, and chloroform/methanol/acetone/acetic acid/water (75:15:30:15:7·5) as the second (Horrocks & Sun 1972). Individual phospholipid classes were identified using iodine vapour, scraped from the plates and the phospholipid content was estimated as inorganic phosphorous after digestion in perchloric acid.

The fatty acid composition of total phospholipids was analysed by gas-liquid chromatography (Firenze *et al.* 1984). An aliquot of erythrocyte membrane was extracted in the presence of 0·1 g/l of 2, 6 di-ter-butyl-4-methyl-phenol as an antioxidant, and the phospholipids were separated from neutral lipids by monodimensional thin layer chromatography with n-hexane/ethylic ether/formic acid (80:20:2) as solvent. Phospholipids were treated with a solution of 3% (w/vol) of methanolic sulphuric acid for 1 h at 80°C. The resulting fatty acid methyl esters were analysed by gas liquid chromatography. Complete separation of fatty acid methyl esters were achieved by programming the temperature of column (180°C for 5 min, temperature rise 2°C/min, final temperature 210°C; injector and flame-ionisation detector temperature was 240°C).

Statistics

Statistical significance of observed difference among groups was calculated by one-way analysis of variance. Results are expressed as mean (SD).

Results

The clinical status of each of the four groups of women studied is summarized in Table 1. There were no differences in mean gestational age. The birthweight of the babies was lower in the proteinuric pregnancy hypertension group ($P < 0·05$) and the only perinatal deaths occurred in this group (two intrauterine deaths).

Routine laboratory findings are shown in Table 2. There

Table 1. Clinical characteristics (at the time of blood sampling) in the four study groups.

Variable	PIH ($n = 20$)	PIH & proteinuria ($n = 10$)	Normotensive pregnancy ($n = 26$)	Non-pregnant ($n = 10$)
Age (years)	30·1 (5·2)	32·0 (2·0)	29·1 (4·8)	30·7 (2·5)
Gestational age (weeks)	34·5 (3·7)	33·5 (4·6)	32·5 (2·4)	—
Blood pressure (mmHg)				
Diastolic	99 (10)	103 (3)	78 (10)	75 (5)
Systolic	48 (13)	153 (4)	116 (10)	110 (10)
Birthweight (g)	2480 (98)	1490 (110)*	3150 (268)	—
Perinatal deaths	0	2	0	—

*$P < 0·05$.

Results are mean (SD) values.

PIH = pregnancy-induced hypertension.

Table 2. Haematological data in the four study groups

Variable	PIH ($n = 20$)	PIH & proteinuria ($n = 10$)	Normotensive pregnancy ($n = 26$)	Non-pregnant ($n = 10$)
Haematocrit (%)	34·2 (3·5)	35·6 (4·6)	34·4 (2·8)	39·5 (4·7)
Haemoglobin (g/dl)	11·2 (1·2)	11·7 (0·6)	11·4 (1·4)	14·5 (0·7)
Red cells ($\times 10^{12}$/l)	3·9 (0·6)	3·6 (0·7)	3·8 (0·3)	4·3 (0·8)
White cells ($\times 10^{9}$/l)	9·0 (1·7)	10·0 (2)	11·9 (3·2)	7·5 (1·5)
Platelets ($\times 10^{9}$/l)	202 (47)	193 (48)	188 (45)	307 (32)
Uric acid (mmol/l)	0·39 (0·05)	0·53 (0·03)*	0·33 (0·05)	0·23 (0·05)
Serum cholesterol (mmol/l)	6·5 (1·3)	7·0 (1·2)	6·3 (0·6)	4·7 (0·3)

Results are mean (SD) values.
PIH = pregnancy-induced hypertension.
*P <0·05

were no statistically significant differences for any of the factors considered between any of the four study groups except for a significantly higher uric acid level in the proteinuric hypertensive pregnancy group (P <0·05).

Lipid composition

Cholesterol content of the erythrocyte membrane was higher in the group with pregnancy-induced hypertension than in the normotensive pregnancies: mean 1·4 (SD 0·6) *vs* 1·0 (SD 0·3) µmol/mg protein (P <0·01), but the phospholipid content did not differ: mean 0·9 (SD 0·3) *vs* 1·1 (SD 0·3) µmol/mg protein. The values in the non-pregnant control group were: mean 1·0 (SD 0·4) and 1·1 (SD 0·4) µmol/mg protein for cholesterol and phospholipids, respectively. This was reflected by a statistically significant increase in the cholesterol/phospholipid molar ratio both in the proteinuric and non-proteinuric hypertensive pregnancies (P <0·05). Interestingly, there was a significant difference between those with and without proteinuria (P <0·01) (Fig. 1).

No correlation was found between membrane cholesterol content and serum levels of total cholesterol (data not shown).

Phospholipid class distribution did not differ significantly between the four study groups (Table 3) nor did fatty acid composition or the ratio of unsaturated to saturated fatty acids (Table 4).

Discussion

Our results have shown an increased cholesterol content of erythrocyte membrane in women with pregnancy-induced hypertension and a concomitant increase in the cholesterol/phospholipid molar ratio. This alteration in membrane lipid composition was not associated with quantitative or qualitative changes in membrane phospholipids nor in the ratio between unsaturated and saturated fatty acids.

Any increase in membrane cholesterol/phospholipid ratio is associated with a decrease in membrane fluidity (Vanderkooi *et al.* 1974). Alteration of the fluidity of the bilayer matrix of the membranes leads to a disturbance of lateral motion of some membrane proteins, which may in turn compromise their biological functions. *In vitro*, the release of potassium and choloride ions from lecithin liposomes and the rate of calcium loss from dioleyl-lecithin vesicles are altered when the cholesterol content of the liposome membrane is high (Papahadjopoulos *et al.* 1967). *In vivo*, cholesterol content of the membrane modulates the activity of ion pumps such as (Na^+-K^+)-ATP triphosphatase (Yeagle 1983). A reduction in the activity of this enzyme has been found in the erythrocytes of hypertensive pregnant women (Tranquilli *et al.* 1988). Increase in erythrocyte intracellular calcium levels, possibly related to alteration of membrane transport system, has also been reported (Sowers *et al.* 1989).

A constant cholesterol/phospholipid ratio which in humans ranges from 0·9 to 1·0 (Cooper *et al.* 1978), is required for the maintenance of cell function. *In vitro* studies of artificial enrichment of erythrocyte membranes with cholesterol have demonstrated that a proportional decrease of cell deformability occurs as a consequence of an increase in the cholesterol/phospholipid ratio, until a maximum cellular rigidity is

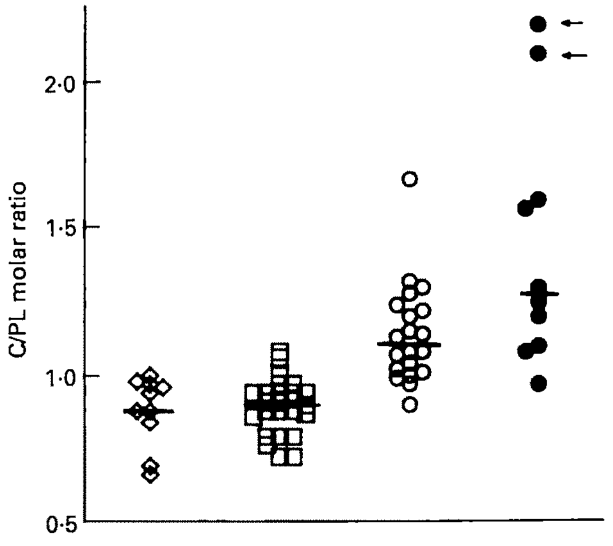

Fig. 1. Cholesterol/phospholipid ratio (C/PL) of erythrocyte membranes in the four study groups. (◇) non-pregnant controls (n = 10, 95% CI 0·79 to 0·96); (□) normotensive pregnant women (n = 26, 95% CI 0·86 to 0·94); (○) women with pregnancy-induced hypertension (n = 20, 95% CI 1·06 to 1·22), (●) women with proteinuric pregnancy-induced hypertension (n = 10, 95% CI 1·13 to 1·74). The horizontal lines represent the mean values for the four groups and the arrows indicate the two pregnancies with intrauterine fetal death.

Table 3. Percentage of phospholipid class distribution in erythrocyte membranes of the groups studied

Phospholipid	PIH ($n = 6$)	PIH & proteinuria ($n = 4$)	Normotensive pregnancy ($n = 10$)	Non-pregnant ($n = 10$)
PC	37·1 (2·9)	35·1 (1·8)	35·2 (4·5)	35·7 (1·7)
PEth	35·0 (5·6)	33·9 (3·9)	34·6 (4·1)	34·6 (0·9)
PS	10·8 (3·1)	11·9 (2·0)	12·3 (3·9)	11·2 (2·0)
PI	5·8 (1·8)	5·1 (0·5)	5·2 (2·5)	6·6 (2·4)
S	10·2 (4·3)	12·7 (2·2)	13·5 (3·4)	12·4 (4·9)

Results are mean (SD) values

Abbreviations: PIH = pregnancy-induced hypertension; PC = phosphatidylcholine, PEth = phosphatidylethanolamine; PS = phosphatidylserine; PI = phosphatidylinositol; S = sphingomyelin.

obtained when the ratio reaches 2·0, above which cell deformability is not further changed (Cooper *et al.* 1978). In our study, the cholesterol/phospholipid ratio was increased in the women with pregnancy-induced hypertension, with values ranging from 1·0 to 2·2. Although we did not analyse cell deformability directly, we assume that a cholesterol/phospholipid ratio between 1·1 and 1·3 would not disturb cell deformability. However, with higher values, and especially with those close to 2·0, an alteration of erythrocyte deformability may have occurred, possibly leading to impaired placental perfusion and inadequate oxygen supply to the fetus. The two pregnancies with a cholesterol/phospholipid ratio above 2·0, were associated with severe placental insufficiency and resulted in intrauterine fetal death.

Fluidity of the cell membranes is also determined by its phospholipid composition. In particular, the increase of phosphatidylcholine/sphyngomyelin ratio and of phospholipid content of unsaturated fatty acid is associated with increased membrane fluidity (Owen *et al.* 1982). The phospholipid classes and their fatty acid composition did not differ among the groups analysed in the present study.

Since the change in the cholesterol/phospholipid ratio in the pregnancy hypertension group was explained only in terms of an increased mass of membrane cholesterol and not by alterations in phospholipid composition, one may speculate that in these patients there is an alteration of membrane homeostasis involving cholesterol. It has been shown that it is possible to increase artificially the cholesterol content of the erythrocyte membrane, by incubating the cells in the presence of cholesterol-rich liposomes (Cooper *et al.* 1978). Since levels of total cholesterol are increased in pregnancy, one may speculate that women with an increased cholesterol/phospholipid ratio might be in fact hypercholesterolaemic. However, no correlation was found between total cholesterol levels and the putative dependent variable cholesterol/phospholipid ratio in the four study groups. Although a direct correlation between serum levels of cholesterol and cholesterol/phospholipid values is excluded, no conclusion can be drawn on the differential role of low density lipid (LDL)- or high-density lipid (HDL)-associated cholesterol or on the presence of an alteration in LDL particles.

The same alteration may occur in other cell types. We have observed similar alterations in platelets from hypertensive pregnant women (unpublished observations). An increase in the cholesterol/phospholipid ratio has also been reported in placental microvilli in pregnancy affected by hypertension (Cester *et al.* 1988), providing evidence for a generalized alteration of membrane composition, involving also the fetal site.

The alteration in the cholesterol/phospholipid ratio

Table 4. Percentage of content of relevant fatty acids and ratio of unsaturated to saturated fatty acids in erythrocyte membrane phospholipids in the four study groups

Fatty acid	PIH & PIH ($n = 6$)	Normotensive proteinuria ($n = 4$)	pregnancy ($n = 10$)	Non-pregnant ($n = 10$)
16:0	24·9 (1·1)	25·9 (2·3)	24·9 (1·8)	21·8 (2·8)
18.0	14·9 (1·3)	15·0 (1·4)	15·9 (1·5)	15·8 (1·5)
18:1	20·5 (2·0)	18·7 (2·6)	20·2 (2·0)	18·8 (3·0)
18:2	9·0 (0·9)	9·7 (0·8)	9·5 (1·0)	9·8 (1·4)
20:1	1·2 (0·5)	1·4 (0·4)	1·7 (0·4)	2·1 (1·1)
20:3	1·3 (0·4)	1·4 (0·7)	1·0 (0·8)	1·0 (0·3)
20:4	15·0 (1·0)	15·1 (0·9)	14·6 (3·7)	17·3 (1·3)
22:4	2·7 (0·6)	2·8 (0·9)	2·9 (0·9)	2·3 (0·8)
22:5	1·7 (0·5)	2·2 (1·0)	1·7 (1·0)	1·6 (0·5)
22:6	4·9 (0·9)	6·3 (1·5)	5·6 (1·3)	5·8 (1·4)
Unsaturated: saturated ratio	1·40 (0·16)	1·39 (0·22)	1·38 (0·19)	1·56 (0·14)

Results are mean (SD) values.

PIH = pregnancy-induced hypertension.

observed in women with pregnancy-induced hypertension may represent a derangement of cholesterol metabolism or of plasma lipoproteins, which predispose to an altered response to the physiological increase of cholesterol levels in pregnancy. This alteration could eventually lead, in the presence of yet unidentified co-factors, to the development of some of the pathophysiological features of pregnancy hypertension, including altered membrane deformability and alteration of certain enzymatic processes.

Further studies are needed to ascertain the role of the cholesterol/phospholipid ratio for screening of pregnant women at risk of developing hypertension, and to examine to what extent this index correlates to the severity of the disease. The correlation between cholesterol content of the membrane and cell deformability needs to be further studied and the alteration of membrane cholesterol found in this condition defined at a molecular level.

Acknowledgments

This work was supported by grants from CNR PF 'Fatma' and 'Aging' (Italy) and by Ministry of University and Scientific and Technologic Research (Fondi 40 e 60%). We are indebted to the nursing staff for the collection of the specimens.

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Received 18 June 1991
Accepted 12 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 508–511

REPRODUCTIVE SCIENCE

Detection of fetal DNA in trans-cervical swabs from first trimester pregnancies by gene amplification: a new route to prenatal diagnosis?

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ABSTRACT

Objective To determine whether fetal sex can be predicted from fetal DNA retrieved transcervically from the lower part of the uterine cavity in the first trimester of pregnancy.
Design Prospective observational study.
Setting St James's University Hospital, Leeds.
Subjects 33 women undergoing legal termination of pregnancy at 9 to 13 weeks gestational age.
Interventions Before termination of pregnancy samples for DNA analysis were obtained with cotton wool swabs from the vagina, cervix and transcervically in 26 women. In the other seven women samples were obtained using a transcervical cell retrieval (TraCeR) procedure involving flushing the lower uterine cavity with 5 ml saline.
Main outcome measures Detection of Y-chromosome specific DNA sequences by the polymerase chain reaction (PCR) in cotton wool swabs taken from the lower uterus in the first trimester of pregnancy to predict fetal sex in comparison with standard cytogenetic analysis. Histological and immunohistochemical analysis of samples obtained by flushing of the lower uterine cavity (TraCeR) to confirm the presence of trophoblast.
Results Fetal sex was predicted accurately in 25 of the 26 pregnancies investigated. Immunohistochemical analysis identified syncytial trophoblast fragments in all seven pregnancies investigated by TraCeR.
Conclusion Trophoblast may be retrieved from the lower uterus in the first trimester by swabs or TraCeR. When purification of these syncytial fragments can be achieved using immuno-magnetic technology, this test will enable prenatal diagnosis of single gene defects in the fetus by the polymerase chain reaction.

The polymerase chain reaction (PCR) has recently confirmed the presence of trophoblastic 'emboli' in maternal peripheral blood during pregnancy (Lo 1989) but the isolation and use of this material for prenatal diagnosis has proved difficult due to the scarcity of fetal cells from this source and extensive contamination by maternal cells (Mueller 1990). An alternative method of trophoblast retrieval is sought which would increase the yield of fetal cells, thereby allowing easier isolation of fetal DNA.

The extra-embryonic membranes surrounding the developing embryo at 6 weeks gestational age are covered by tertiary chorionic villi. By 12–14 weeks gestation, only the villi of the chorion frondosum remain; the villi at the ab-embryonic pole having regressed to leave the smooth chorion leavae. Shettles (1971) and Rhine (1975) postulated that degenerating villi may shed cells into the lower pole of the uterus and cervical mucus and that these cells may be retrieved for analysis. Samples retrieved from the endocervix proved negative in most studies but identifiable trophoblast cells were recovered from the lower part of the uterine cavity. However, culture of these cells proved unreliable (Rhine *et al.* 1975, 1977; Goldberg 1980) and the technique was abandoned.

We report that Y-chromosome specific target sequences can be detected in samples retrieved from the lower uterus in pregnancies containing a male fetus by the polymerase chain reaction. We also describe a modified method of trans-cervical sampling which is more likely to yield intact syncytial trophoblast fragments allowing the prospect of purification using immuno-bead separation techniques. The implications of these findings for the prenatal diagnosis of single gene defects in the fetus are discussed.

Subjects and methods

This study was approved by the medical ethics committee of St. James' University Hospital, Leeds. Patients were inter-

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viewed before first trimester termination of pregnancy by a research registrar who explained the nature and purpose of the study and obtained written consent.

Sample collection

Two prospective methods of trophoblast retrieval were assessed. In the first, 26 women were studied under general anaesthesia before termination of pregnancy when cotton wool swabs were used to take specimens from the vagina, cervix and trans-cervically from a point 1 cm beyond the internal cervical os. Ultrasound was employed to confirm that the fetus was alive and to provide visual guidance when taking the trans-cervical swab. Termination of pregnancy was then carried out and the aborted material was retrieved for karyotyping.

The second method of trans-cervical sampling was investigated in a further seven women. A flexible, hollow plastic trocar was introduced into the lower part of the uterine cavity under ultrasound control (Embryo Transfer Catheter, Rocket of London, Ltd). A fine cannula was passed through the trocar to protrude 1 cm into the lower uterine cavity and 5 ml of physiological saline were instilled and retrieved for analysis. We refer to this procedure as trans-cervical cell retrieval (TraCeR).

Polymerase chain reaction

The amplification of a 150 base-pair (bp) Y-chromosome specific repeat sequence was as described by Kogan *et al.* (1987) after digestion of cellular material from swabs with proteinase K (Kawasaki 1990). Polymerase chain reaction products were resolved by electrophoresis in 1·8% agarose gels with ethidium bromide staining. Controls included male and female DNA and water blanks. All reactions were carried out in triplicate.

Cytogenetics

Standard cytogenetic procedures were used to obtain chromosome smears and male cells were identified by short-arm counting and giemsa banding. Karyotype results were not accessible to the workers performing the polymerase chain reaction for prediction of fetal sex.

Identification of trophoblast

Samples obtained by TraCeR were resuspended in 100 μl complete medium (RPMI 1640 containing 10% heat inactivated fetal bovine serum) and smeared onto clean glass slides. After air drying overnight, smears were fixed in acetone for 10 min at room temperature. Smears of TraCeR samples were then labelled with a panel of monoclonal antibodies (MoAbs) which were reactive with human trophoblast. The antibodies employed were: CAM 5·2 (Becton Dickinson, CA, USA) which is directed against low molecular weight cytokeratins and has been reported to react with all villous and extravillous trophoblast populations (Makin *et al.* 1984); NDOG1 (Seralab, Crawley, UK) showing specific reactivity with villous syncytiotrophoblast and with chorionic villous mesenchyme in early pregnancy and is directed against hyaluronic acid (Sunderland *et al.* 1985); FT1.41.1 (kindly provided by Professor P. M. Johnson, University of Liverpool) showing specific reactivity with villous syncytiotrophoblast and villous mesenchyme in first trimester placentas (Johnson P. M., Bulmer J. N., unpublished results); and HMFG1 (Unipath, Bedford, UK) which is directed against an epithelial membrane antigen and labels endometrial epithelial cells but is generally unreactive with first trimester trophoblast (Bulmer & Johnson 1985). Samples were also labelled with Dako-LC (Dakopatts, High Wycombe, UK) which is directed against CD45 and reacts with all leukocytes. Using this panel of antibodies it was possible to identify trophoblast as well as endometrial epithelial cells and leucocytes.

All smears were labelled by an avidin-biotin-peroxidase technique using a Vectastain Elite kit (Vector Laboratories, CA, USA). Negative controls included omission of primary antibody and replacement with an irrelevant mouse MoAb. A sample smear of each specimen was also stained with haematoxylin and eosin to allow morphological assessment.

Results and discussion

The polymerase chain reaction analysis was performed on DNA extracted from the cotton swabs and a typical result is shown on Fig. 1. Of the 26 pregnancies in our study, nine male fetuses were predicted by polymerase chain reaction detection of Y-chromosome specific DNA sequences (cases 5, 8, 9, 12, 16, 18, 19, 20, 26 in Table 1) of which eight were confirmed by standard cytogenetic analysis; one was not confirmed due to culture failure and one male fetus (no. 21) was not detected by the polymerase chain reaction. This failure may have been due to insufficient fetal DNA being retrieved or to the inhibition of Taq polymerase by substances which could be removed by further purification of the DNA (de Franchis 1988). One of the triplicate samples from the uterine swab gave a positive signal (no. 23) although the fetus was female by cytogenetic analysis. As each triplicate was carried out on DNA extracted from individual swabs, we believe this to have been a false-positive result, illustrating the need for multiple assays and for minimizing the risk of extraneous contamination (particularly, in this case, from male handlers).

To control for the specificity of our analyses, the polymerase chain reaction was also carried out on DNA extracted from endocervical and vaginal swabs. Considering the greater number of pregnancies containing female fetuses in our cohort, we found that positive signals from endocervical samples were more frequent when the fetus was male. This suggests that there had been passage of trophoblast material into the cervical canal. Despite negative signals from the uterine swab and negative cytogenetic analyses, positive signals were occasionally obtained from endocervical and vaginal swabs (nos. 10, 11, 17, 23). Although women were selected on the basis that they had abstained from intercourse for at least 3 days preceding the termination, the most likely explanation for these results is contamination of the swabs by residual spermatozoa following intercourse. That this did not affect the polymerase chain reaction prediction is shown by comparing subjects 13 and 14. In the former, eight positive signals out of a possible nine were obtained from the three sites and the fetus was designated male by cytogenetic analysis. In the latter,

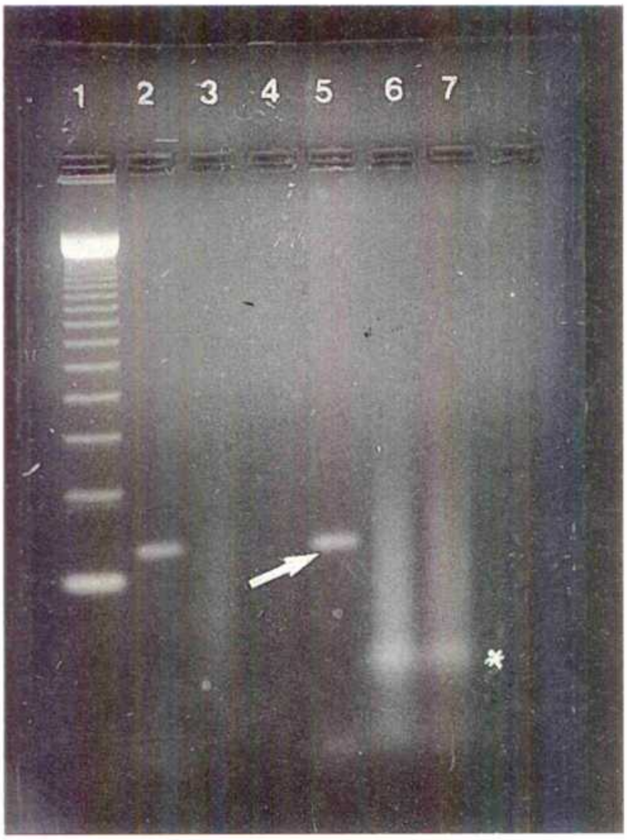

Fig. 1. Analysis of polymerase chain reaction (PCR) amplification (see text for method). Track 1, step-ladder of DNA fragments comprising multiples of a minimum 123 bp. Track 2, male DNA. Track 3, female DNA. Track 4, water blank. Tracks 5–7, uterine (5), endocervical (6) and vaginal swabs (7) retrieved from a patient with a male pregnancy. The presence of the 150 bp male-specific product is clearly visible in the control sample (track 2) and uterine sample (track 5-arrowed). The bands marked with an asterisk in tracks 6 and 7 are non specific products of this PCR reaction.

endocervical and vaginal sites gave all-positives while the uterine sample was all-negative and the fetus was designated female by cytogenetic analysis. Taken together therefore, the data suggest that the uterine swab is a reliable source of fetal material and that there is a minimal risk of extraneous DNA contamination provided that the described method is followed.

The seven samples obtained by the TraCeR procedure provided further proof that our swab-based polymerase chain reaction data came from fetal material. Syncytial clumps were identified in all smears obtained by TraCeR (Fig. 2a). Although the cellularity of smears varied, syncytial elements were identified in all smears at a minimum frequency of one syncytial clump per low power field (×6·3 objective ×10 eyepiece). Immunohistochemical studies confirmed that the syncytial elements noted in haematoxylin and eosin stained sections were trophoblast, showing reactivity with CAM 5·2, NDOG1 and FT1-41·1 (Fig. 2b).

As indicated in Fig. 2a, the TraCeR procedure has the added advantage over the swab sampling method of yielding intact trophoblast syncytial fragments. This method could therefore be further developed in order to segregate trophoblast from maternal contaminants using highly specific antibodies recognizing trophoblast surface antigens, coupled to magnetized beads. Prior to segregation of trophoblast, samples retrieved by swabs or TraCeR could be utilized for prediction of fetal sex and for the detection of paternally derived aneuploidy. Of considerable interest, however, is that trophoblast that was essentially free of maternal contaminants following immuno-bead separation, would yield fetal DNA suitable for polymerase chain reaction amplification of target sequences without the need for culture. This would facilitate the rapid diagnosis of single gene defects for which DNA probes have been developed, with the homozygote being distinguished from heterozygote using standard blotting techniques.

The atraumatic retrieval of trophoblast from the lower uterine segment by TraCeR might provide a safer and earlier first trimester diagnosis than chorionic villus sampling (CVS) during which the placental bed is subject to direct trauma and possible inoculation with micro-organisms. Moreover, the recent MRC European trial comparing CVS with conventional genetic amniocentesis has given cause for concern by suggesting that CVS is less safe, an adverse pregnancy outcome occurred more frequently in the CVS group with 4·6% fewer women having a successful outcome (MRC Working Party on the Evaluation of Chorionic Villus Sampling 1991).

Further concern over the safety of CVS has emerged following a report that oromandibular-limb hypogenesis syndrome and transverse limb defects may occur more frequently following CVS when performed at earlier gestations (Firth

Table 1. Comparison of the polymerase chain reaction (PCR) and cytogenetic analyses. Three amplifications per sample were carried out and scored + for the presence of the 150 base-pair (bp) product or − for its absence

Subject no.	Gestation (weeks)	Cytogenetics	PCR detection of male DNA		
			Uterus	Endocervix	Vagina
1	8	Female	−−−	−−−	−−−
2	10	Female	−−−	−−−	−−−
3	12	Female	−−−	−−−	−−−
4	12	Female	−−−	−−−	−−−
5	9	Male	+++	++−	+−−
6	11	Female	−−−	−−−	+−−
7	10	Female	−−−	−−−	−−−
8	12	Male	+++	+−−	+−−
9	10	Male	+++	+−−	++−
10	11	Female	−−−	+−−	++−
11	13	Female	−−−	+−−	+−−
12	9	Female	−−−	−−−	++−
13	12	Male	+++	+−−	−−−
14	12	Female	−−−	−−−	−−−
15	12	Female	−−−	−−−	−−−
16	13	Male	+++	++−	+++
17	13	Female	−−−	+++	+++
18	9	Male	+++	−−−	+−−
19	9	Culture failed	+++	−−−	+−−
20	11	Male	+++	−−−	−−−
21	10	Male	−−−	−−−	−−−
22	11	Female	−−−	−−−	−−−
23	11	Female	+−−	+++	+−−
24	12	Female	−−−	−−−	−−−
25	12	Female	−−−	−−−	−−−
26	9	Male	+++	+++	−−−

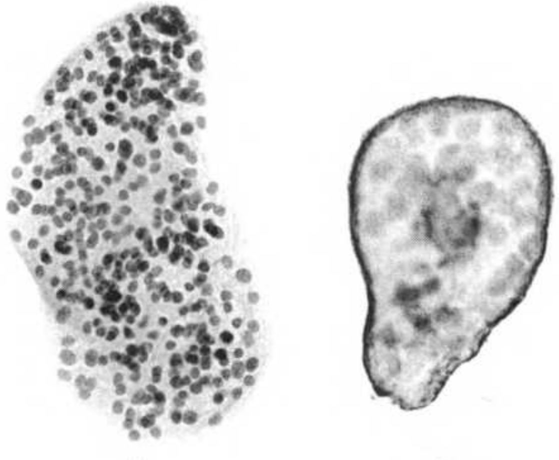

Fig. 2. Smear preparations of TraCeR sample (a) stained with haematoxylin and eosin showing a typical syncytial cell group (magnification ×250); (b) labelled by an avidin-biotin-peroxidase technique with CAM 5·2 (directed against low molecular weight cytokeratins) showing membrane and cytoplasmic reactivity (magnification ×400).

1991). Alternative methods for the early and safe retrieval of trophoblast for the prenatal diagnosis of chromosomal defects in the fetus are being sought. Early amniocentesis is currently being assessed, but it is unlikely to give a first trimester diagnosis and may increase the risk of pulmonary hypoplasia (Hislop 1984). The TraCeR procedure therefore warrants further clinical investigation to more fully assess its efficacy as a source of fetal tissue for polymerase chain reaction-based prenatal diagnosis of single gene defects. However, the potential of this test will be enhanced when a molecular method of detecting Down's syndrome is developed that will not need cell culture. We are attempting to develop such a test in our department.

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Received 4 June 1991
Accepted 24 November 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 512–515

REPRODUCTIVE SCIENCE

Cord insulin and C-peptide—distribution in an unselected population

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ABSTRACT

Objective To assess the distribution of cord blood insulin in an unselected population, and examine its relation to birthweight centiles.
Setting District General Hospital in Nottinghamshire.
Subjects 209 unselected singleton births.
Mean Outcome Measure Cord blood insulin; cord blood C-peptide; birthweight centiles.
Results Hyperinsulinaemic babies (>97th centile for cord insulin) were found at all birthweight centiles. 15% of high birthweight babies were hyperinsulinaemic. For low birthweight babies, the distribution of cord insulin/C-peptide was skewed indicating a high number of low values. Hypoinsulinaemic babies were present up to the 50th centile for birthweight.
Conclusions Abnormalities of fetal insulinisation may be found in babies of all birthweights.

Abnormalities of fetal growth that result from abnormal substrate availability are marked by degrees of insulinisation of the fetus (Spellacy *et al.* 1987; Weiss *et al.* 1984). The typical hyperinsulinaemic macrosomic newborn of the hyperglycaemic mother is well recognized, as is the hypoinsulinaemic growth retarded newborn. These abnormalities are readily identified in infants at the extremes of birthweight centiles but there is now much interest in metabolic causes of growth abnormalities within the centile ranges 10%–90% for gestational age. There has been a tendency to regard any newborn in this range as 'normal' even if body mass indices raise the possibility of accelerated or retarded growth in the third trimester. To provide a basis for diagnostic testing of insulinaemia in the newborn we have studied an unselected population from a non-teaching hospital district. Normal ranges of cord insulin have been constructed against birthweight centiles.

Subjects and methods

Cord vein blood was collected from the placental end of the cut cord at delivery from 209 unselected singleton births (gestational age range 34–42 weeks) at Bassetlaw District General Hospital. None of the women was known to be diabetic. Specimens were centrifuged in the delivery suite and plasma pipetted and stored at −20°C. Where haemolysis had occurred only C-peptide was measured (O'Rahilly *et al.* 1984). In non-haemolysed specimens both C-peptide and insulin were measured.

C-peptide and insulin were measured by radioimmunoassay, C-peptide using a kit supplied by Guildhay Antisera, Guildford, Surrey, and insulin by an in-house second antibody method using guinea pig antisera from Guildhay and iodinated insulin IM38 from Amersham International, Amersham, Bucks, and Gamma-B precipitating antisera from IDS, Washington, Tyne and Wear.

Coefficients of variation, inter and intra-assay for insulin were 7·4% and 6·8% respectively and for C-peptide 8·5% and 6·4% respectively.

Birthweight centiles are those of Gairdner & Pearson (1985).

Statistical analysis

For the whole sample and for each of the grouped birthweight centiles box and whisker plots were constructed of both insulin and C-peptide levels in cord plasma. The 10th, 25th, 50th, 75th and 90th centile of cord insulin and C-peptide levels was calculated for each birthweight centile. Spearman rank correlation coefficient was used to assess the effect of birthweight centile on cord insulin and cord C-peptide.

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Results

Cord C-peptide was measured in 209 samples and cord insulin in 129.

The box and whisker plot distribution for C-peptide against birthweight is shown in Fig. 1 and for insulin in Fig. 2. The median values and ranges are reported in Table 1. There was a weak positive correlation between increasing birthweight and cord insulin and C-peptide ($r = +0{\cdot}22$ insulin; $r = +0{\cdot}18$ C-peptide). For babies with birthweights under the 10th centile the distribution was skewed to the left, indicating a high number of low values. For babies with birthweights above the 90th centile, the distribution was skewed towards the higher values. In the 129 pregnancies where both cord insulin and C-peptide were measured, the Spearman rank correlation coefficient was 0·73.

Discussion

The relation between insulinisation of the third trimester fetus and birthweight is well recognised (Spellacy *et al.* 1987; Weiss *et al.* 1984; Lin *et al.* 1981). Fetal insulinisation is a major determinant of birthweight but probably exerts its effects on energy stores rather than somatic length or head circumference. Susa *et al.* (1979) demonstrated a 34% increase in body weight in a hyperinsulinaemic fetal rhesus monkey with no significant increase in length. There was a significant increase in size of placenta, heart, liver and spleen but not in lungs, brain or kidneys. Milner & Hill (1973) suggest that this differential effect of insulin may be because somatic cellular growth is occurring near to its maximum in the normal fetus and most excess energy can only be stored as adipose tissue.

Spellacy *et al.* (1987) measured umbilical vein and artery insulin levels in 71 women. Their sample included a number of insulin dependent diabetics who were not reported separately. They found a mean insulin of 23·8 μU/ml in newborns with birthweights above 4000 g and 10·4 μU/ml in those weighing less than 2500 g. They do not comment in detail on the intermediate birthweight group.

Lin *et al.* (1981) noted a correlation between small for gestational age, appropriate for gestational age and large for gestational age infants in both cord insulin and C-peptide levels measured in 103 subjects. Some selection took place as diabetics were excluded and an effort was made to identify small fetuses before delivery for inclusion in the protocol.

Weiss *et al.* (1984) reported a normal range for cord insulin, based on 180 infants with a birthweight under the 90th birthweight centile from which obese mothers, actual and potential diabetics had been excluded. They reported centiles of cord insulin as follows: 3rd, 10th, 50th, 90th and 97th: 1·4, 4·3, 8·8, 15·4, 17·7 μU/ml respectively. In a separate study of babies with birthweights above 4000 g they reported that 25% had cord insulin above 20 μU/ml. They suggested this cut off might be used as a diagnostic marker for metabolic disturbances of growth associated with maternal hyperglycaemia.

We report the distribution of cord insulin and C-peptide for an unselected population including large for gestational age babies. Our findings confirm previous reports of a positive correlation between cord insulin/C-peptide and birthweight centile.

We did not observe the clear lack of overlap between C-peptide levels for different centile groups described by Lin *et al.* (1981).

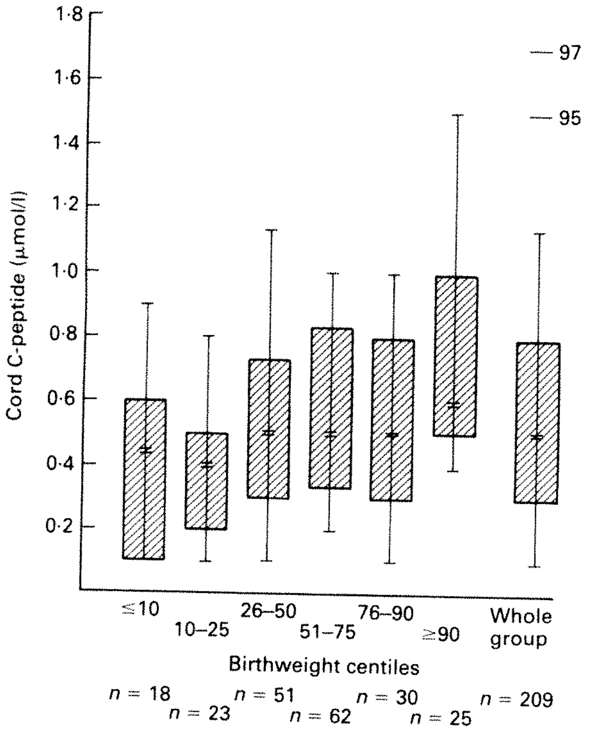

Fig. 1. The relation between cord C-peptide (μmol/l) and birthweight centile for gestational age. — median; ▨ interquartile range; I 10th–90th centile.

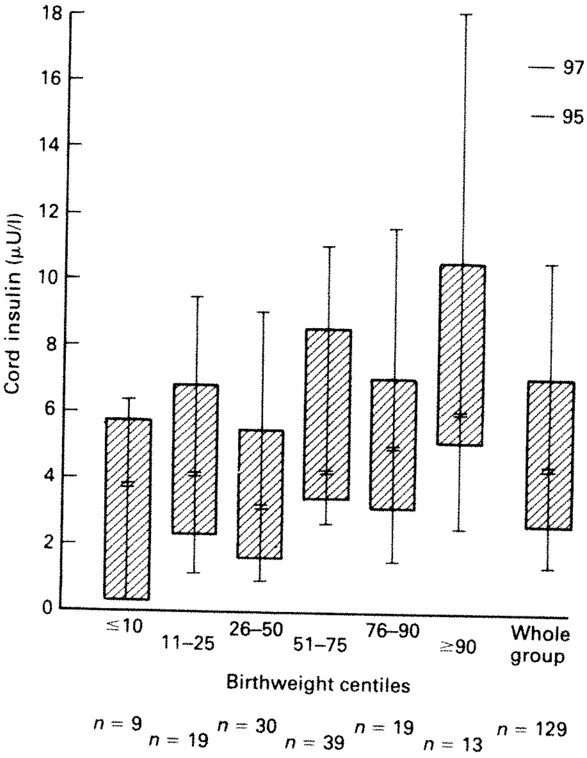

Fig. 2. The relation between cord insulin (μU/l) and birthweight centile for gestational age. — median; ▨ interquartile range; I 10th–90th centile.

Table 1

Birthweight centile group	C-peptide (µmol/l) (*n*=209) Median (range)	Cord insulin (µU/l) (*n*=129) Median (range)
<10	0·45 (0·1–2·3) (*n* = 18)	3·7 (1·6–21·5) (*n* = 9)
11–25	0·4 (0·1–2·5) (*n* = 23)	4·1 (1·1–19) (*n* = 19)
26–50	0·5 (0·1–1·8) (*n* = 51)	3·0 (0·5–16·5) (*n* = 30)
51–75	0·5 (0·1–3·5) (*n* = 62)	4·3 (1·5–16) (*n* = 39)
76–90	0·5 (0·1–1·6) (*n* = 30)	5·0 (1·5–13·8) (*n* = 19)
>90	0·6 (0·1–1·8) (*n* = 25)	6·0 (1·6–21·5) (*n* = 13)

Weiss *et al.* (1984) reported that 25% of babies with crude birthweight above 4000 g had cord insulins above the 97th centile for babies born at less than 4000 g, which he suggested reflected disordered carbohydrate metabolism as the cause of macrosomia in 25% of high birthweight babies. We have analysed our data using the same criteria and shown that three babies out of 14 (21%) with birthweight at or above 4000 g had cord insulins above the 97th centile for babies weighing less than 4000 g. Thus our findings are compatible with those of Weiss *et al.* (1984) in this respect. For reasons that are not apparent, C-peptide fails to discriminate in this way, despite its good correlation with insulin levels. We consider that construction of a 'normal' range should be based on an unselected population. We suggest that a normal range based on birthweight centiles is of more clinical relevance than one based on crude birthweight alone.

Using our data we have shown that two babies out of 13 (15%) above the 90th centile for birthweight (or two babies out of 14 weighing 4000 g or more) have cord insulins above the 97th centile for the whole population (16·5 µU/ml). We suggest that this proportion reflects the true frequency of disordered carbohydrate metabolism in high birthweight babies.

Infants with cord insulin or C-peptide above the 97th centile for the whole group could be considered hyperinsulinaemic. Whilst the majority of these babies are of high birthweight, the hyperinsulinaemic baby is also found in all birthweight centiles (Figs. 3 and 4). Thus, although the typical hyperinsulinaemic baby at risk of neonatal hypoglycaemia is large for gestational age, hyperinsulinaemia is also observed in some babies of appropriate weight for gestational age.

Hypoinsulinaemia is a feature of asymmetrical intrauterine

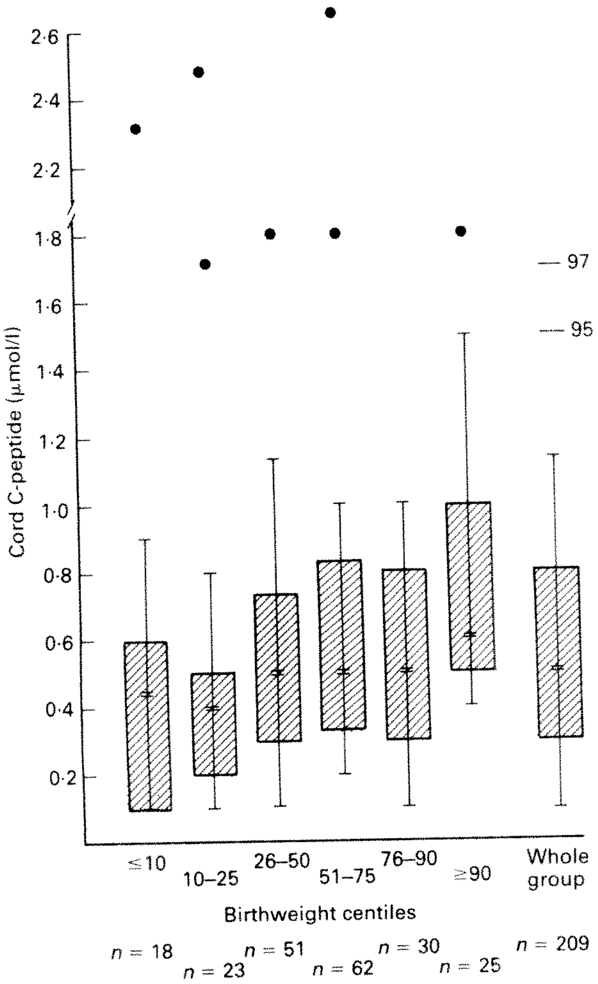

Fig. 3. The relation between cord C-peptide (µmol/l) and birthweight centile for gestational age showing the birthweight centiles of hyperinsulinaemic babies (see text). — median; ▨ interquartile range; I 10th–90th centile.

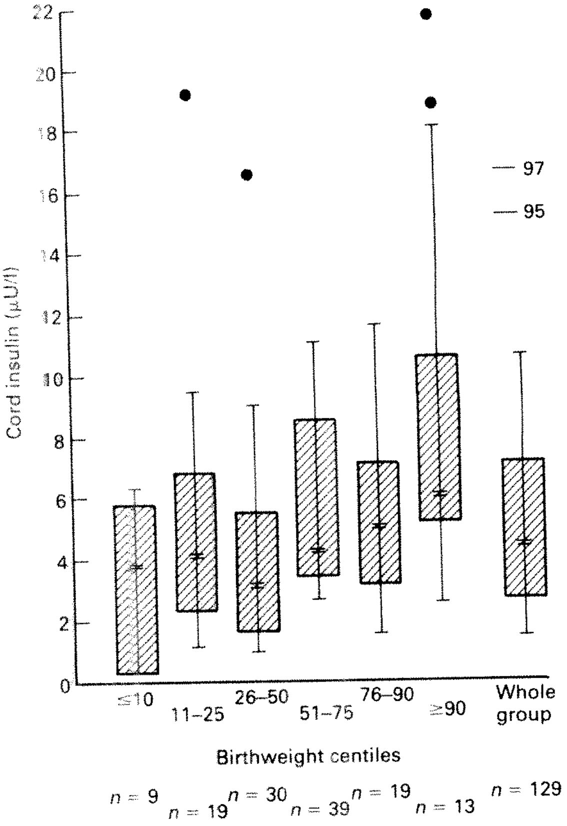

Fig. 4. The relation between cord insulin (µU/l) and birthweight centile for gestational age showing the birthweight centiles of hyperinsulinaemic babies (see text). — median; ▨ interquartile range; I 10th–90th centile.

growth retardation. Our results indicate that relatively hypo-insulinaemic infants occur in each of the birthweight centile groups albeit more frequently in those below the 10th centile. This can be explained by intrauterine growth retardation in babies who fail to achieve their potential weight despite achieving apparently appropriate weight for gestational age.

Confronted by a normal weight baby of inappropriate body mass index, stored cord plasma may be used to explore the relation to intrauterine metabolic events.

Studies of fetal insulinisation in pregnancy using amniocentesis or cordocentesis may be valuable in the future in identifying abnormal states which may respond to maternal therapy or justify early obstetric intervention.

Acknowledgments

We are grateful to the consultants in Obstetrics and Gynaecology, to Sister Whitehead and her midwifery colleagues and the Department of Clinical Chemistry at Bassetlaw General Hospital for help with collection and storage of the specimens.

The manuscript was typed by Gillian Burkinshaw.

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Received 17 April 1991
Accepted 16 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 516–517

CASE REPORT

Spinal muscular atrophy and pregnancy

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Case report

Patient 1

A 22-year-old woman in her first pregnancy had been diagnosed to have spinal muscular atrophy at age 8. Prepregnancy weight was 36·6 kg (80 lb) and her weight at delivery was 46·7 kg (103 lb). Her height was 150 cm (59 inches). She has used a wheelchair since age 14.

Onset of her muscular problems was at age 5 with weakness and difficulty walking. Her symptoms have been gradually progressive over the last 15 years. She indicated increased weakness on her left side and in her upper extremities, with loss of muscle bulk in her lower extremities during this time.

Neurological consultation during the pregnancy supported the diagnosis of type III Kugelberg-Welander juvenile spinal muscular atrophy. Neurological examination showed that the cranial nerves were normal. There was mild weakness of neck flexion but extension was normal. There was generalized wasting of the upper and lower extremities, more in the lower than in the upper limbs. In the lower extremities, proximal power was graded at 2/5 and distally 3/5. In the upper extremities, proximal power was graded as 3/5 and, distally, 4/5. Sensory examination was normal. Reflexes were absent with the exception of a trace response from the biceps and triceps, bilaterally. Gait was characterized by very exaggerated swinging of the pelvis with an increased lumbar lordosis. The patient could walk 2 or 3 steps only without support. There was no bowel or bladder dysfunction.

There was no other significant medical, surgical or family history.

The pregnancy was uneventful with normal fetal growth. There were no respiratory or urinary tract problems.

The patient was admitted in active labour and progressed to full dilatation with the fetus in the left occiput transverse position. The first stage of labour was 6 h 25 min and second stage 4 h 24 min.

Caesarean section with epidural anaesthesia was required because of cephalopelvic disproportion. There were no operative or post-operative problems.

The male infant was completely normal with appropriate size for gestational age (weight 3140 g) with Apgar scores of 7 at 1 min and 9 at 5 min.

The puerperium was uneventful but she stayed in hospital longer than average to allow her to become able to care for her baby from her wheelchair. Breast feeding was encouraged but she decided she would prefer to use artificial feeding.

Patient 2

A 22-year-old woman in her first pregnancy had been diagnosed as having spinal muscular atrophy at age 7. Pre-pregnancy weight was 41 kg (93 lb) and her weight at delivery was 58 kg (127 lb). Her height was 160 cm (63 inches).

Motor development as an infant and young child had been delayed and walking had occurred at 3 years. The patient had required several procedures to lengthen the achilles tendon to correct her toe walking. As a child and teenager, she was able to ride a bicycle and swim. She remained ambulatory without the use of a cane or walker. Her weakness was progressive until age 16 and had been stable since that time. She coped with walking on flat surfaces but had difficulty climbing stairs.

Neurological consultation during the pregnancy supported the diagnosis of type III Kugelberg-Welander juvenile spinal muscular atrophy. Neurological examination showed the cranial nerves were normal. There was no wasting or weakness of neck flexures or extensors. She had wasting of shoulder girdle muscles bilaterally, with marked wasting of all arm, forearm and hand muscles. Her legs were extremely thin, with marked wasting of thigh and lower leg muscles. She walked with a wide-based waddling gait and had accentuated lumbar lordosis. She had global weakness symmetrically involving both proximal and distal limb muscles. The deltoids and hip abductors were relatively spared. Reflexes were absent. Sensory examination was normal. There was no bowel or bladder dysfunction.

There were no other significant medical, surgical or family history.

The pregnancy was uneventful, with normal fetal growth. She was admitted to hospital at 33 weeks gestational age for bedrest because of painless shortening and dilatation of her cervix. There were no respiratory or urinary tract problems.

At 37 weeks labour was induced with artificial rupture of membranes and oxytocin infusion. The first stage of labour was 5 h. The second stage of labour was 1 h and vacuum extraction was used to assist maternal effort. She gave birth to a male infant (weight 3100 g) with Apgar scores of 9 at 1 min and 10 at 5 min. The puerperium was uneventful and breast feeding was successful.

Discussion

Pregnancies in women with spinal muscular atrophy are

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uncommon. Spinal muscular atrophy is a subdivision of anterior horn cell disease. Maternal muscular weakness may complicate delivery and mobility during pregnancy. Recommendations for delivery and the genetic risks for the fetus must be considered.

Kugelberg-Welander juvenile spinal muscular atrophy type III (Baraister 1985) has an onset between 3 and 17 years. Proximal muscles are more affected than distal muscles. Onset is gradual. Hip muscles are usually the first muscles involved, leading to difficulty in walking and climbing stairs and shoulder weakness can occur. Confinement to a wheelchair is usual by 35 years of age. The facial and tongue muscles are rarely involved. Mental retardation is not associated with this condition. Bowel and bladder function is not impaired.

A single report (Dietz & Gigon 1989) described a 35-year-old woman with a chronic form of spinal muscular atrophy and four completed pregnancies over a 5-year period. These pregnancies were aggravated by recurrent cystitis. In all four pregnancies, the patient had a caesarean section followed by severe respiratory problems. Three of the four children showed a striking muscular hypotonia postpartum which disappeared soon after the neonatal period.

The inheritance of spinal muscular atrophy has been reported in pedigrees as recessive, dominant and X-linked. Autosomal recessive inheritance may account for over 90% of spinal muscular atrophy (excluding type I) with onset before age 14. Onset is before age 5 and usually before age 2 (Pearn *et al* 1978). Our two patients had negative family histories and are more likely to have a recessive form of spinal muscular atrophy, although new autosomal dominant mutations cannot be ruled out. The molecular genetic mutation or chromosomal location is not known for this condition. It is not possible to distinguish autosomal recessive from dominant inheritance in isolated cases. No carrier or prenatal testing is available. The risk of the two children developing type III spinal muscular atrophy for the two reported pregnancies is estimated at 10% (Pearn & Walton 1978) due to the possibility of a new dominant mutation in the probands.

Our two patients demonstrate that uterine function is adequate and that full dilatation can be achieved. Second stage intervention was required for both of them. In one, maternal weakness with an appropriate fetal presentation allowed vacuum extraction. The second required a cesarean section because of cephalopelvic disproportion with small maternal stature.

Our patients had no respiratory or urinary tract problems, although such problems are common in the non-pregnant individuals with spinal muscular atrophy.

Epidural anaesthesia was used for both deliveries. If general anaesthesia is required, succinylcholine should be avoided. It is a depolarizing muscle relaxant and may cause prolonged action and hyperkalaemia. Respiratory function would need to be monitored carefully after general anaesthesia.

Assessment of the facilities in the woman's home is an important part of care, as modifications to the home and nursery may be necessary. Furniture such as the crib, changing table, and bath facilities, need to be altered to allow mothers with spinal muscular atrophy the opportunity to participate safely in the care of the baby.

Acknowledgments

We would like to thank Dr R.D. Keyes, Dr G. Gibson and Dr G. McMorland for their medical opinions and Ms D. McPherson for secretarial assistance.

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Received 12 November 1991
Accepted 15 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 518–523

SHORT COMMUNICATIONS

Vaginal ultrasound in donor insemination

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The introduction in 1988 of compulsory screening of donors for the human immunodeficiency virus (HIV) has necessitated the exclusive use of quarantined frozen semen for donor insemination. This has resulted in a 50% reduction in fecundability compared with the use of fresh semen. Consequently, to improve fecundability rates accurate timing of insemination has become a priority (Shapiro 1991). The methods commonly used include basal body temperature (BBT) charts, assessment of cervical mucus and recently urinary luteinizing hormone (LH) kits. By enabling home monitoring, LH kits are an advantage to women living in scarcely populated areas, reducing the number of visits to the clinic each month.

The ability of LH kits to predict ovulation was found by some to be superior to BBT charts and cervical mucus timing (Yong *et al.* 1989; Lucciano *et al.* 1990; Grinstead *et al.* 1989). Others have found BBT charts and cervical mucus timing as good as LH kits (Kossoy 1989; Fehring 1990). However, the effect of LH kits on fecundability rates is not clear. Barratt *et al.* (1989) compared timing on a previous BBT chart with a urinary LH kit, and found fecundability rates were 0·04 and 0·07 respectively, a difference which was not statistically significant. In a similar study Federman *et al.* (1990) compared one insemination timed with an LH kit, with two when timing was based on previous BBT charts, and found fecundability rates of 0·12 and 0·05 respectively, again not statistically significant. In complete contrast, Odem *et al.* (1991) found fecundability rates of 0·06 and 0·13 for LH kits and BBT charts, respectively. In view of these conflicting results, we decided in addition to use ultrasound to confirm the presence of a potentially ovulatory follicle and adequate endometrium before insemination. Vaginal ultrasound is ideal for such assessment, it is quick, well tolerated and accurate (Yee *et al.* 1987). We report the results of the first 118 ultrasound scans performed between December 1990 and June 1991 in 100 different women.

Subjects and methods

The women were instructed to test their morning urine from day 10 of a 28-day cycle (or the equivalent day for longer or shorter cycles) for the LH surge (Clearplan One Step, Unipath Ltd) and to attend the clinic on the first day of any detectable change.

At the clinic the cervical mucus (Insler) score was determined. A score of >10 had been required previously for insemination (maximum score 12). Then, using an Aloka SS-500 machine with a 5 MHz vaginal probe, ultrasonic assessment was performed before treatment. All follicles >5 mm were measured. Only those women with a leading follicle >18 mm and an endometrial thickness >9 mm were inseminated (Marinho *et al.* 1982). If a pre-ovulatory follicle (<18 mm) was present, the woman was asked to attend the following day for a further scan before insemination. All women were asked to attend for a plasma progesterone assessment on day 21, a level >25 nmol/l was considered to confirm that ovulation had occurred.

Results

After the ultrasound scan only 77 women (65%) were treated that day (group 1) and 74 (96%) of them attended for plasma progesterone estimations on day 21, all of which were in the ovulatory range. Five women (4%) in group 1 would not have been inseminated if Insler scoring and LH kit alone had been used. With the addition of an ultrasound scan all five were inseminated and all had ovulatory progesterone values.

The other 41 women (35%) were not inseminated as a result of the ultrasound findings (group 2). Thirty-one (76%) of these attended for plasma progesterone estimations. Donor insemination was not performed in group 2 for the following reasons.

Of the 41 women 21 (51%) had post ovulatory ultrasonographic appearances, which was confirmed in 18 by the subsequent progesterone measurements (three did not attend for progesterone measurement). Of these 21 women nine had Insler scores of >10 and would have been inseminated previously using Insler scoring and LH kit alone.

In 10 women (24%) pre-ovulatory (<18 mm) follicles were present (range 14·5–17·5 mm), with an adequate endometrium. In eight of these a further scan was possible the next day and in all eight follicular growth to >18 mm had occurred and insemination was performed. Day 21 plasma progesterone confirmed ovulation in seven of these eight women (one woman did not attend). Nine of the ten would have been inseminated on the first day of attendance using Insler scoring and the LH kit alone.

In 7 (17%) a combination of poor follicle size combined with an inadequate endometrium was found and the cycle abandoned. Five of these attended for day 21 progesterone measurement and all were anovulatory. One of these five would have been inseminated using Insler scoring and LH kit alone.

In 3 (7%) the endometrium alone was inadequate, (range

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0–7 mm) despite a potentially ovulatory follicle. Only one of these three women attended for progesterone estimation, which confirmed ovulation. All three had Insler scores <10 and would not have been inseminated.

If insemination had been timed using our previous combination of Insler scoring and the LH kit, only 76% of inseminations would have been correctly timed, with 20% (19/118) performed when conditions were unfavourable.

Pregnancy rate

Before the use of ultrasound to aid in the timing of donor insemination our fecundability rate was 0·05. The fecundability rate during the first 6 months after the introduction of ultrasound was 0·11.

Discussion

This study demonstrates the advantage of ultrasound scans before insemination. Up to 15% of women attending for donor insemination based on an LH kit alone have already ovulated and probably should not be inseminated. A further 10% have other factors detectable by ultrasound sufficient to defer or postpone insemination in that cycle.

Using ultrasonography, others have demonstrated spontaneous ovulation before a rise of urinary LH in 9–12% (Lloyd & Coulman 1989; Elkind-Hirsch *et al.* 1986). The number of women in these reports was small (n=33, n=16 respectively). Our figure of 15% is similar to these reports. However, with the benefit of a larger series and, in addition, assessment of the endometrium we identified a further 10% in whom insemination should be delayed or postponed. If one includes those without day 21 progesterone results then 35% (41/118) were not inseminated as a result of the addition of ultrasound.

These results may explain the apparent failure of LH kits alone, to improve conception rates.

Following The Human Fertilization and Embryology Act 1990 and the possible decline in donors, artificial insemination clinics may be obliged to avoid insemination when conditions are unfavourable, thus conserving semen. The usage of urinary LH kits offers a practical advantage to certain women. However, their ability to improve pregnancy rates remains disputed and these kits should not be regarded as the best indicators for timing. When possible other methods should be employed as an adjunct, to aid in the timing of insemination.

Although not readily available in many clinics, a vaginal ultrasound scan before insemination is quick and acceptable to the women. It can determine those in whom treatment should be given, should not be given and those in whom it should be delayed.

Acknowledgments

We would like to thank Miss A. Carruthers S.R.N., H.V.C. and Mrs V. MacPherson R.G.N.

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Received 10 September 1991
Accepted 23 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 520–521

Polycystic ovaries in association with müllerian duct anomalies

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It has been suggested that müllerian duct anomalies are more common in women with infertility (Nickerson 1977, 19% major anomaly in 190 women), oligomenorrohea (Stampe Sorenson 1987) and the polycystic ovary syndrome (PCOS) (Tzingouis *et al.* 1978). The diagnosis of PCOS was based on the demonstration of bilateral ovarian enlargement either by laparoscopy or laparotomy. No one has described a uterine anomaly in association with ultrasound diagnosed PCOS. With the advent of high resolution ultrasound scanning it is now possible to diagnose polycystic ovaries more easily and tissue diagnosis, which is invasive and may lead to tubal damage, is no longer necessary.

We reviewed all the women presenting to our reproductive endocrine clinic who had ultrasound diagnosed polycystic ovaries with the aim of identifying those with major müllerian duct anomalies.

Subjects and methods

Ovaries are described as polycystic if there are 10 or more cysts, 2–8 mm in diameter, arranged around a dense stroma or scattered throughout an increased amount of stroma (Adams *et al.* 1985). Women are described as having PCOS or the Stein-Leventhal syndrome when the ultrasound appearance of PCO is associated with symptoms that can include oligomenorrohea, amenorrohea, hirsutism, acne and infertility. Conway *et al.* (1989) emphasized the heterogenity of patients with PCOS and recommended ultrasound as the best means of diagnosis. In our unit all patients have an ultrasonic assessment of uterine shape and size (transabdominally, transvaginally or both), together with a measurement of endometrial depth at the same time as their ovarian ultrasound.

We found two women with major müllerian duct anomalies in 1512 women with PCOS (prevalence 0·13%). The first woman presented at 17 years with primary amenorrohea. She also had hypothyroidism and was treated with thyroxine. Gonadotrophins, prolactin and karyotype were normal. Ultrasound scan demonstrated a small uterus (40×4 mm) deviated to the right with an enlarged polycystic right ovary (43×27×18 mm) and a left pelvic kidney. Treatment with oestradiol failed to induce uterine growth and she remained amenorroheic. At laparoscopy, a uterine remnant was found on the right side in association with a normal fallopian tube and ovary. The left tube, ovary and cervix were absent. An intravenous pyelogram confirmed a functioning left pelvic kidney.

The second woman presented at 27 years having had oligomenorrohea, hirsutism and acne for 2 years. She had a uterus didelphys with a double cervix and double vagina (Fig. 1). Ultrasound scan identified classically polycystic ovaries. An intravenous pyelogram demonstrated a single pelvic kidney on the right side with a single ureter. Follicle stimulating hormone levels were 4·1 U/l, luteinizing hormone 13·7 U/l and testosterone 3·1 nmol/l. A short synacthen test (tetracosactrin 250 µg intravenously) suggested heterozygosity for 21-hydroxylase deficiency.

Discussion

It is difficult to estimate the true prevalence of müllerian duct abnormalities as such anomalies often fail to present clinically (DeCherney & Dlugi 1984). The prevalence of major anomalies is said to range from 0·1–1·0% (Philpott & Ross 1954; DeCherney & Dlugi 1984), although Nasri *et al.* (1990) found a higher prevalence of 3% in 300 patients who had vaginal as opposed to abdominal ultrasound. As far as PCOS is concerned, two case reports have described an association with müllerian duct anomalies (Stampe Sorenson & Balslev 1987; Rahbarnia 1976). Tzingounis *et al.* (1978) noted an increased prevalence (3·2%) of major anomaly in 254 patients with Stein-Leventhal syndrome. Most patients with oligomenorrohea have PCOS (Adams *et al.* 1986) and Stampe Sorenson

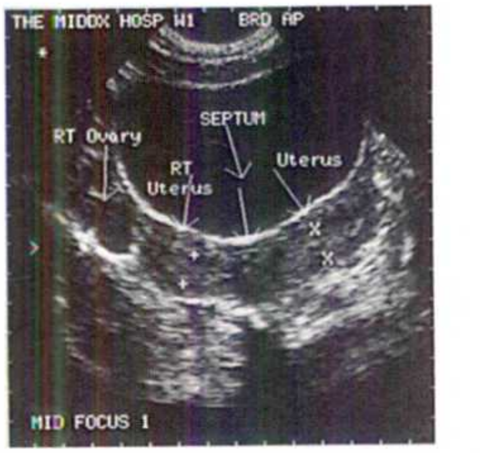

Fig. 1. Transverse section through the uterine fundus (Patient No. 2, transabdominal scan). Two uterine cavities can be seen with a central septum. The crosses mark the separate endometria.

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(1987) noted an increased prevalence (7%) of major müllerian duct anomalies in patients with oligomenorrohea. In contrast, Shearman (1968) suggested that ovarian function was usually normal in patients with an absent uterus and vagina.

Both cases were associated with renal anomalies and underlines the importance of renal assessment in all patients with major müllerian duct anomalies, Mercer *et al.* (1981) cite a 11%–20% prevalence of renal anomalies in association with uterine malformations.

The association of polycystic ovaries with both classical 21-hydroxylase and non-classical late onset congenital hyperplasia has been reported previously (Hague *et al.* 1989). The second patient appeared heterozygous for congenital adrenal hyperplasia rather than having late onset, non-classical adrenal hyperplasia (Hague *et al.* 1989). An association of adrenal hyperplasia with uterine anomalies has not been reported previously.

Ultrasonography is a valuable tool avoiding the necessity for invasive procedures, and can be used to diagnose müllerian duct anomalies as well as polycystic ovaries. From our experience the prevalence of major müllerian duct anomalies in patients with PCOS (0·13%) is similar to that recorded in the general population and suggests that contrary to previous reports, the association is likely to be coincidental.

Acknowledgments

We would like to thank Mr N. C. Siddle MRCOG, Consultant Obstetrician and Gynaecologist, who performed the laparoscopy on the first patient.

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Received 15 April 1991
Accepted 16 December 1991

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 521–522

Maternal serum alpha-fetoprotein levels in pregnant women with gestational diabetes

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Pregnant women with insulin-dependent diabetes mellitus tend to have lower serum alpha-fetoprotein (AFP) levels than the norm (Milunsky *et al.* 1982, Wald *et al.* 1979). The reason is not known.

Based on our own observations of individual pregnancies, we had the impression that women who developed gestational diabetes in the course of pregnancy had lower maternal serum AFP levels than the norm. The aim of this study was to clarify whether the initial stages of the diabetic metabolic condition influenced the maternal AFP level as early as the beginning of the second trimester.

Patients and Methods

In a retrospective analysis, maternal serum AFP levels determined between 16 and 18 weeks gestation were compared for 53 consecutively selected women with gestational diabetes from a hospital population (diabetes group) and a control group of 560 healthy pregnant women selected in a random

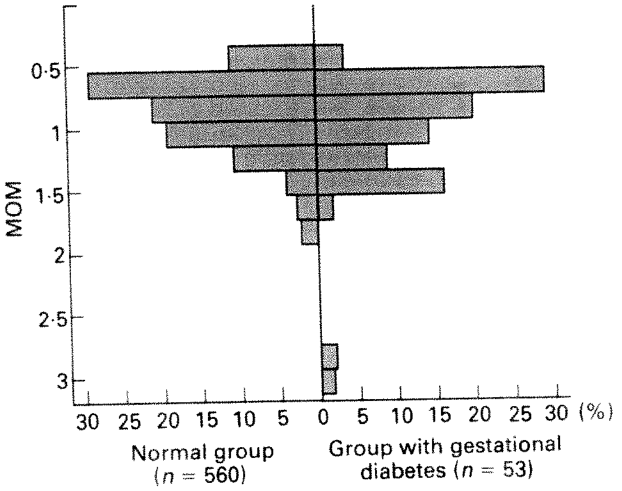

Fig. 1. Relative frequency histograms of maternal serum alpha-fetoprotein levels expressed as multiples of the median (MOM) in 53 women with gestational diabetes and 560 healthy women.

sample from a general population. The presence of gestational diabetes had been confirmed with an oral 100 g glucose tolerance test (GTT) (Freinkel 1985).

Since serum AFP level increases between 15 and 20 weeks gestation, the levels were expressed as multiples of the median (MOM) for purposes of comparison.

For statistical analysis, the Mann-Whitney test was used, and the results were calculated with the Statview™ statistical program (Abacus Concepts Inc).

Results

Fig. 1 presents the data graphically by a pair of relative frequency histograms aligned vertically. The median of the MOM values was 0·89 in the control group and 0·90 in the diabetes group. There was no statistically significant difference between the two groups ($Z = 0{\cdot}98$, $P = 0{\cdot}32$).

Discussion

Our findings did not confirm the hypothesis that women with gestational diabetes have lower AFP levels than normal.

There are no reports on whether or not the initial stage of gestational diabetes already has an influence on AFP metabolism in the early second trimester.

At least in the first trimester, gestational diabetes does not seem to have any adverse effects on the occurrence of congenital malformations (Chung *et al.* 1975). To improve the accuracy of the interpretation, some authors recommend adjusting maternal serum AFP values to take account of ethnic group, the presence (or absence) of insulin-dependent diabetes, and bodyweight (Haddow *et al.* 1981; Johnson *et al.* 1984; Macri 1986; Macri *et al.* 1987; Milunsky *et al.* 1982; Shapiro *et al.* 1975; Wald *et al.* 1981; Wald *et al.* 1979). Since women with gestational diabetes tend to weigh more, and heavy women tend to have lower AFP levels (Haddow *et al.* 1981; Johnson *et al.* 1984; Wald *et al.* 1981), it was expected that the diabetes group would have lower AFP levels, but since our results showed nearly identical AFP levels in both groups, no adjustment was made for maternal weight.

On the basis of our results we conclude that maternal serum AFP levels in the early second trimester do not differ significantly between women with gestational diabetes and women with normal pregnancies.

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Received 16 October 1991
Accepted 25 February 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 522–523

Laparoscopic tubal manipulating forceps for extrusion of early ectopic pregnancy

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Treatment of tubal ectopic pregnancy by operative laparoscopic surgery has been practised for a number of years (DeCherney & Diamond 1987), and has proved to be equally safe and effective when compared to laparotomy, with the

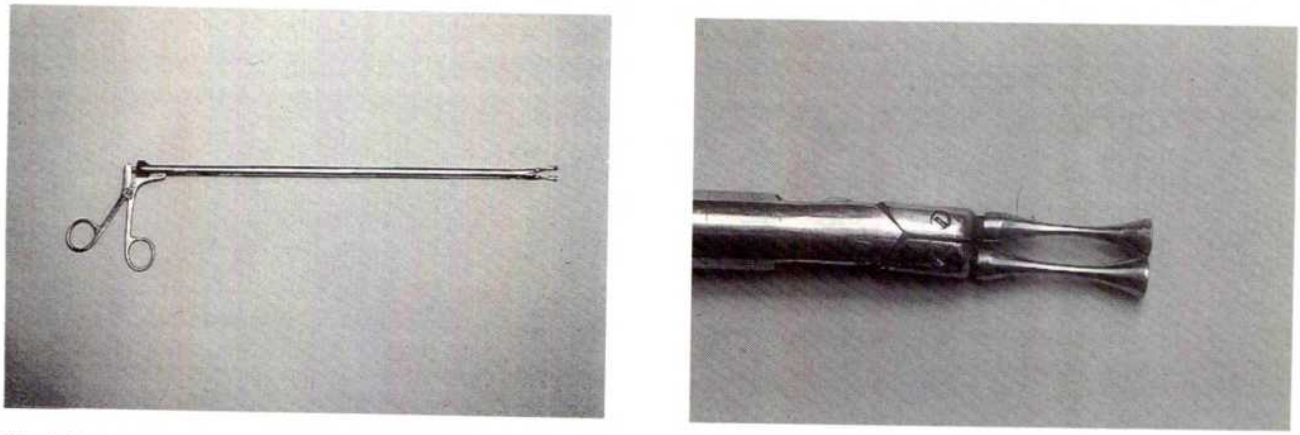

Fig. 1. Design of laparoscopic tubal manipulating forceps.

advantages of reduced hospital stay and minimal scarring (Brumsted *et al.* 1988). The affected tube is usually either excized completely (Schwartz & Martin 1985), or incized with diathermy or the neodymium-yttrium-aluminium-garnet laser with removal of the ectopic pregnancy (Hallatt 1990). Alternatively, the lesion may be injected under direct vision with methotrexate or other toxic solutions (Pansky *et al.* 1991). Most enthusiasts believe that approximately 80% of tubal ectopic pregnancies can be dealt with laparoscopically, although haemoperitoneum greater than 500 ml, shock, or lesions over 3 cm in diameter are considered contraindications by most authorities (Silva 1988).

During laparotomy for early ectopic pregnancy, it is sometimes possible to 'milk' a small (10 mm diameter) out of the distal end of the tube, thus avoiding surgical trauma. The instrument described here was designed to combine this technique with the laparoscopic approach, allowing atraumatic extrusion of small ectopic pregnancies without resorting to salpingotomy.

Device and Method

The laparoscopic tubal manipulating forceps are a 12 mm diameter instrument designed for insertion into the peritoneal cavity via a suitable bore trochar and cannula. The distal end of the device consists of two 'dumbbell' shaped rollers mounted on freely revolving spindles, hinged proximally and opposable (Fig. 1). The distal edges of the rollers in the closed position are 2 mm apart to avoid crushing the mesosalpinx.

In the opinion of the author, good quality video equipment with a high definition colour camera, is essential. The entry port should be established on the affected side, as laterally as possible, to allow optimal geometry for the 'sweeping' movement required to extrude the pregnancy. 5 ml of 1% lignocaine with 1:100 000 adrenalin is injected via a fine gauge spinal needle under direct vision into the antimesenteric border of the tube around the affected site. The assistant manipulates the uterus in a position of maximum anteversion and angulated away from the affected side in order to place the affected tube 'on stretch'. The forceps rollers are then closed around the tube medial to the pregnancy, and using a sweeping motion, the pregnancy is extruded into the peritoneal cavity. There should be little or no bleeding if adrenalin has been injected first. The pregnancy may then be removed using either forceps or suction. A tubular drain may be placed laparoscopically if necessary.

Comment

This device is a useful addition to the already impressive range of laparoscopic instruments available for minimally invasive gynaecological surgery. Conservative laparoscopic treatment of ectopic pregnancy is highly effective, and there is evidence that the majority of conserved tubes become patent (Keckstein *et al.* 1990). There is no evidence that such surgery predisposes to further ectopic pregnancy in the affected tube (Hallatt 1990). It may therefore be the case that the treatment of choice for early tubal pregnancy is laparoscopic extrusion, or if this proves impossible because of size, laparoscopic excision.

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Received 9 December 1991
Accepted 14 January 1992

British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 524–526

BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting on 8 September 1991 at Stranmillis College, Belfast

Laparoscopic treatment of early endometrial carcinoma by J. A. M. Broadbent and A. L. Magos. Minimally Invasive Therapy Clinic, Academic Department of Obstetrics & Gynaecology, The Royal Free Hospital, Pond Street, London, NW3 2QG.

Endometrial carcinoma presents as Stage I, grade 1 disease in over 40% of affected patients. As the incidence of lymph node metastases is about 2% in these early, well differentiated tumours and almost zero in tumours <2 cm in diameter at hysteroscopic assessment, a simple hysterectomy with bilateral salpingo-oophorectomy is the generally accepted initial treatment. Furthermore, women with endometrial carcinoma are usually elderly and obese, and one third have associated medical disorders such as hypertension, cardiac disease and diabetes mellitus. Ideal management should therefore not include a laparotomy with its higher morbidity, laparoscopically assisted vaginal hysterectomy should be applicable to these patients. Advantages include (a) superior visibility of the abdominal cavity, (b) ability to take peritoneal washings, (c) easy removal of the adnexa using bipolar electrocoagulation, (d) mobilization of the uterus and adnexa in the presence of adhesions, and (e) division of the uterosacral ligaments to aid descent of the uterus when prolapse is not present. Using three 5·5 mm suprapubic punctures, the infundibulopelvic and round ligaments are desiccated using bipolar electrocautery and divided with scissors. In the presence of adequate prolapse the surgeon can then perform the remainder of the operation as for routine vaginal hysterectomy. If not the following steps can be continued laparoscopically. The uterovesical fold of peritoneum is grasped and opened using scissors, and the bladder reflected down using a combination of atraumatic grasping forceps and hyrodissection. The broad ligament is then further divided down to the level of the uterine vessels, which are desiccated and divided. Finally, the posterior peritoneum, uterosacral and transverse cervical ligaments are divided posteriorly using bi- and monopolar electrocautery. The uterus can then easily be removed through the introitus, and the remainder of the procedure completed vaginally. Following vault closure, laparoscopy is repeated to ensure haemostasis.

Biochemical evidence for compensated ovarian failure in women with unexplained menorrhagia by J. M. Eldred, W. Edridge and E. J. Thomas. Newcastle General Hospital, Newcastle-upon-Tyne NE4 6BE.

Daily assessments of plasma or salivary concentrations of pituitary and ovarian hormones during one menstrual cycle were used to investigate ovarian function in 46 women with the subjective symptom of regular but unacceptably heavy menstrual loss. All of these women had previously undergone a dilatation and curettage examination which revealed no abnormality. Their endocrine profiles were compared with similarly derived data from 47 normal volunteers. Anovulatory cycles in both groups were excluded from the analysis. The menorrhagic group ($n = 41$) had significantly higher follicle stimulating hormone ($P < 0{\cdot}01$) and oestradiol concentrations ($P < 0{\cdot}01$) in the follicular phase and lower luteal phase salivary progesterone concentrations ($P < 0{\cdot}05$), when compared with the control group ($n = 43$). These studies are consistent with a state of compensated ovarian failure in the menorrhagic group. The two groups were not, however, age matched and the differences observed may reflect reproductive ageing rather than the pathogenesis of unexplained menorrhagia. There was no relation between individual or averaged values of pituitary or ovarian hormones and objectively measured menstrual loss. Subsequent hysterectomy has indicated the presence of gynaecological pathology in many of the study group emphasizing the poor specificity of blind diagnostic curettage in detecting an homogeneous group.

The role of oestrogen in the treatment of postnatal depression by A. Henderson, A. Gregoire,* A. Kumar* and J. Studd. *Institute of Psychiatry, London and Dulwich Hospital, London.

An hormonal aetiology for postnatal depression has long been suggested, although, despite much research, no clear association between sex hormone levels or activity and mood has been found. Nevertheless, in view of the successful role of oestrogens in the treatment of premenstrual syndrome and climacteric depression, we are currently conducting a double-blind, placebo-controlled study to assess the effects of oestrogen in postnatal depression. Women up to 18 months post-partum who are suffering from depression, with a score of >14 on the Edinburgh Post Natal Depression Scale (EPDS), and onset within 12 weeks post-partum are being recruited. Baseline measures include the EPDS, a standardized diagnostic interview giving an RDC diagnosis, and validated measures of marital satisfaction and social support. Subjects are then randomized either to receive active treatment comprising 6 months treatment with oestradiol skin patches—delivering 200 µg oestradiol/24 h with dydrogesterone, 10 mg/day, for 12 days added in months 4, 5, and 6; or placebo treatment comprising placebo skin patches and placebo progesterone. Subjects in both groups are followed up 4 weekly over the 6 month treatment period and for 3 months thereafter. Progress measures include the EPDS, the diagnostic interview and daily symptom charts. Independent preliminary analysis of results from the first 37 women recruited are available. Three women in the active group and 10 in the placebo group have dropped out. The results have shown a statistically significant difference in drop out rates between the two groups; a significant improvement in the self-rating EPDS scores in the active group compared to placebo at one month; a low incidence of adverse effects (<5%) and oestradiol levels in the active group in the mid-physiological range. In view of these encouraging preliminary results, we hope to complete the study within 6 months and thus assess fully the efficacy and safety of oestrogen therapy in the treatment of postnatal depression.

Retinoic acid modulate RAR expression in cultured endometrial stroma by A. Prentice, C. J. Matthews, C. P. F. Redfern and E. J. Thomas*. University of Newcastle-upon-Tyne, and *Department of Human Reproduction/Obstetrics, University of Southampton.

Retinoic acid (RA), a derivative of vitamin A, has marked effects on development and cell differentiation. It acts through nuclear receptors similar in structure to steroid and thyroid hormone receptors. We have reported previously the presence of three retinoic acid receptors (RAR_a, RAR^b, RAR^i) in both endometrial glands and stroma. It has been reported that in some malignant cell lines, the expression of RAR_b is induced by RA and we have asked whether or not this is true of primary cultures derived from endometrial stroma. Normal endometrium was separated into its stromal and epithelial components by collagenous digestion and filtration. Stromal cell cultures were treated with all trans RA at concentrations of 10^{-7}, 10^{-9} and 10^{-10}M for between 1 and 24 h. Induction of RAR^b ^{m}RNA occurred by 4 h and was concentration dependent. This induction was not inhibited by elevating ^{c}AMP levels within the cells or by treating the cultures with ^{c}AMP analogues. To establish whether this induction was dependant upon *de novo* protein synthesis, cells were treated with cycloheximide, a protein synthesis inhibitor, at a concentration of 1 µg/ml. Induction of RAR^b was apparently independent of protein synthesis but cycloheximide itself also induces some expression of RAR^b. No induction of RAR^a or RAR^i was observed. These results show that RA modulates expression of RAR^b in cultured endometrial stromal cells.

The effect of an oxytocin antagonist (CAP 476) on calcium mobilization in single cultured myometrial cells by S. Thornton,* J. L. Gillespie, W. Dunlop* and J. R. Greenwell. Department of Physiological Sciences and *Obstetrics, University of Newcastle-upon-Tyne, NE2 4HH.

Oxytocin initiates a rise in intracellular calcium, $[Ca_{2+}]^i$, which precedes uterine contraction. This is due to an influx of extracellular calcium $[Ca^{2+}]_0$, via receptor operated channel and release of stored intracellular calcium. The mechanism of action of the oxytocin antagonist, CAP 476, is not known. The present communication investigates the effect of CAP 476 on (i) the oxytocin induced increased in $[Ca^{2+}]_i$, (ii) voltage sensitive calcium influx, and (iii) spontaneous calcium influx. Cells were isolated from myometrial biopsies obtained at hysterectomy and grown in tissue culture. Fluorescence techniques (Fura-1; excitation 350/380 nm, emission 520 nm) were used to determine changes in $[Ca^{2+a}]_i$, in single cells. Application of oxytocin (10^{-7}M) caused a transient rise in $[Ca^{2+}]_i$. Perfusion of CAP 476 (2 µM; $n = 6$) completely prevented the oxytocin induced rises in $[Ca^{2+}]_i$. This was reversed by the removal of CAP 476. Since the oxytocin induced increase in $[Ca^{2+}]_i$ was completely eliminated, both the influx of $[Ca^{2+}]_0$ and the release of intracellular stores must be prevented. Perfusion of 120 nM K^+ causes membrane depolarization leading to influx of calcium through voltage operated calcium channels. CAP 476 did not prevent the increase in $[Ca^{2+}]_i$ on application of K^+ thereby demonstrating that the antagonist has no effect on calcium influx through voltage operated calcium channels. A small proportion of cultured myometrial cells develop spontaneous transient increases in $[Ca^{2+}]^i$ without antagonist stimulation. The frequency of these was reduced by CAP 476 demonstrating that even in the absence of exogenous oxytocin, myometrial contractility may be reduced. We have demonstrated that CAP 476 prevents the oxytocin induced increase in $[Ca^{2+}]_i$ but does not prevent the influx of calcium through voltage operated calcium channels. CAP 476 reduces the frequency of spontaneous calcium transients which occur in the absence of agonist stimulation.

What happens to fetal oxygenation if the mother is given oxygen via a face mask? by H. McNamara and N. Johnson. University Department of Obstetrics and Gynaecology, University of Leeds.

It is common to see obstetricians react to an abnormal cardiotogram (CTG) by giving the mother 28% oxygen via a face mask. The almost instantaneous resolution of the imagined fetal distress is often taken as evidence that maternal oxygen therapy affects the fetus within minutes. Until the development of the fetal pulse oximetry it has been impossible to investigate the observation in humans and we have had to extrapolate data from animal models, cross sectional studies and experiments using tissue oxygen electrodes. Fetal scalp pulse oximeters provide a non-invasive measurement of oxygen delivery to the fetal brain. In 12 successful longitudinal duplicated case studies the effect of maternal oxygen administration on fetal arterial oxygenation was investigated with a scalp pulse oximeter. Stringent criteria for data quality were imposed and signals were only accepted if pure signal (purity >90%) was recorded. Poor and mediocre quality data were discarded by an observer blinded to oxygen therapy. Our results showed that 28% oxygen therapy to the mother has no effect on fetal oxygenation, 40% oxygen via face mask had a small effect on the fetus but this effect was not observed until the mother had been on oxygen therapy for at least 10 min. The only significant rise in fetal oxygenation occurred after 10 min when the mother was given 100% pure oxygen by an anaesthetic face mask. Fetal oxygenation remained high for 5 min after therapy. Obstetricians are deluding themselves when they believe that 28% oxygen via face mask cures a fetal distress within minutes, although 100% maternal oxygen via face mask does improve oxygenation but this effect does not occur for at least 5 mins.

Possible role of serotonin in pregnancy induced hypertension by J. C. Cooper, G. M. Filshie, P. V. Maynard, C. Hutter, G. Robinson, P. Singh and P. Rubin. Department of Obstetrics and Gynaecology, Queen's Medical Centre, Nottingham.

The cause of hypertension in pregnancy is multifactorial. We believe that serotonin has a central role, being released by platelet dense granules promoting systemic vasospasm and platelet aggregation. 5-hydroxy-indoleacetic acid (5-HIAA) is the main metabolite of serotonin. A 24 h urine collection (taken into a bottle containing HCl) was taken from 19 normotensive pregnant women and 13 pregnant women with pregnancy-induced hypertension (PIH). This was then analysed for 5-HIAA using gas chromatography-mass spectometry. Urinary 5-HIAA was significantly greater in the PIH group than in the normotensive controls. There was a significant difference between the two groups for the concentration of 5-HIAA, the 5-HIAA concentration per gram of creatinine (which corrects for any error in collection) and the total 24 h excretion ($P<0{\cdot}001$; $P<0{\cdot}005$; $P<0{\cdot}05$, respectively, using the Mann-Whitney U statistical analysis). There was no statistical difference between the two groups for maternal age, gestation, parity or 24 h urinary volume. This study lends further support to the hypothesis that serotonin is a mediator in the pathogenesis of PIH.

The influence of ovarian cysts on IVF cycles related to serum steroid levels by J. M. Jenkins, D. W. Davies, F. W. Anthony, P. Wood and G. M. Mason. Department of Obstetrics & Gynaecology, University of Southampton, BUPA Chalybeate & Princess Anne Hospitals, Southampton.

Reviewing 780 in vitro fertilization (IVF) cycles, where buserelin was commenced in the preceding luteal phase and human menopausal gonadotrophin on day 4 of the ensuing menses, 53 cycles were identified with sonolucent cysts (30–50 mm diameter). Of the latter 53 cycles, the serum oestradiol was significantly greater on day 4 in 22 cycles abandoned for poor follicular development than in 31 cycles which proceeded to oocyte retrieval (median 407, range 28–2238 pmol/l *vs* median 129, range 18–577 pmol/l, $P<0{\cdot}05$), but the corresponding day 4 serum androstenedione levels were similar (median 5·3, range 1·6–9·9 nmol/l *vs* median 5·2, range 2·8–8·8 nmol/l). There was little evidence of persistent corpus luteal activity, with day 4 serum progesterone <5 nmol/l in all but one woman. Of the 31 cycles proceeding to oocyte retrieval 9 had a day 4 serum oestradiol >200 pmol/l (95th centile for day 4 oestradiol in patients without apparent cysts) and these cycles produced a significantly lower ($P<0{\cdot}01$) percentage of grade 1 embryos than the 22 cycles with day 4 oestradiol ≤200 pmol/l, 17% (of total 41) *vs* 47% (of total 134). The six conception cycles had a day 4 serum oestradiol ≤200 pmol/l. Functional activity of ovarian cysts is associated with an adverse influence on IVF cycles.

The home pad test by Eboo Versi. Department of Obstetrics & Gynecology, The Royal London Hospital, London.

The aim was to assess the new home pad test for patient compliance, ease of administration, reproducibility and accuracy when compared with video-urodynamics. Overall 127 patients were assessed: a symptoms questionnaire, examination, midstream urine specimen, uroflowmetry, video-urodynamics and a 48 h home pad test with frequency volume chart. A total of 80 patients had a repeat pad test to study reproducibility. The test was easy to use for both patient and doctor. The reproducibility was better for the 48 h than for the 24 h test. However, this could be further improved by adjusting for frequency volume chart ($r = 0{\cdot}86$, regression constant = 0·01, regression coefficient = 0·01). Compared with video-urodynamics the accuracy of the pad test was good (Kappa = 0·67; sensitivity = 0·92) but there was a high false positive rate. Eleven patients had normal video-urodynamics but were incontinent on pad testing; six of these women had repeat video-urodynamics and five were found to have detrusor instability implying that the pad test may be detecting occult instability. The excellent reproducibility implies that this test can be used reliably as a non-invasive means of monitoring the effect of treatment. Given the recently appreciated high false negative rate for cystometry, these results would suggest that incontinent patients (pad testing) with negative cystometry should not be assumed to have genuine stress incontinence.

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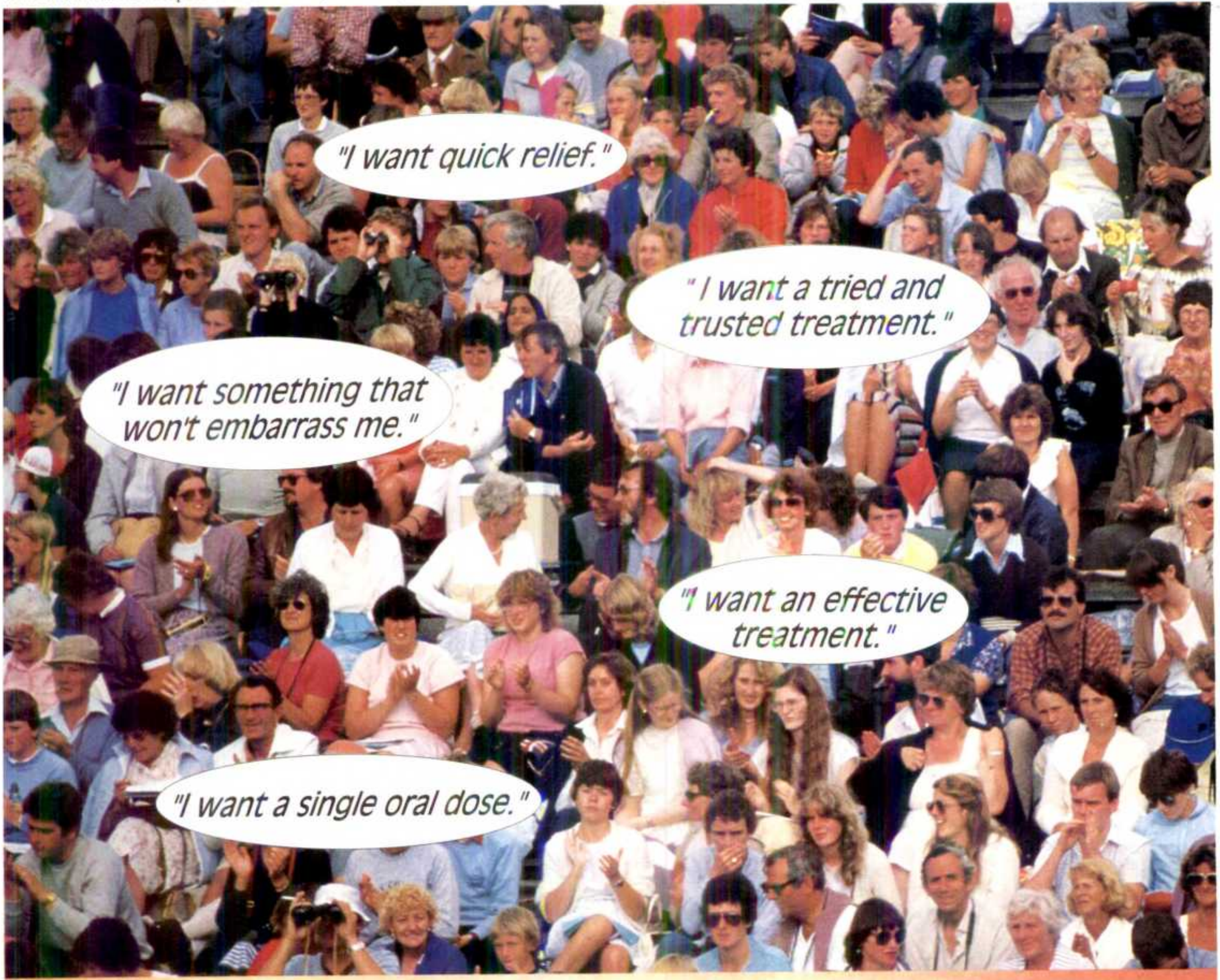
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British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 527–532

CORRESPONDENCE

Doppler investigation of uteroplacental blood flow resistance in the second trimester: a screening study for pre-eclampsia and intrauterine growth retardation

Dear Sir,
Bewley *et al.* (1991) underestimate the potential value of uterine artery Doppler studies as a screening test for abnormal pregnancy outcome. Their definition of an abnormal waveform is too rigid and the endpoints of adverse pregnancy outcome are incomplete. A review of the published literature on the outcome of pregnancies complicated by reduced uteroplacental perfusion reveals the following four abnormal outcomes:

Pre-eclampsia. Robertson *et al.* (1967) first described the pathological lesions of the spiral arteries in pre-eclampsia. Steel *et al* (1990) found that those patients with a single abnormal uterine artery waveform, showing a high resistance pattern at 24 weeks gestation had a significantly higher risk of hypertension in later pregnancy than those with normal waveforms.

Placental abruption This is more likely to complicate a pregnancy with pre-eclampsia (Abdella *et al.* 1984). Uzan *et al.* (1989) found that abnormal uterine artery Doppler flow waveforms preceded placental abruption by 3–4 weeks in the majority of their patients.

Intrauterine growth retardation (IUGR). The same vascular disease of the placental bed that occurs in pre-eclampsia is seen in pregnancies with IUGR without pre-eclampsia (DeWolf *et al.* 1980). Steel *et al* (1990) found that patients with an abnormal uterine artery waveform at 24 weeks gestation had increased risk of an infant with asymmetrical IUGR.

Preterm delivery. Naeye (1989), in a study of placentas from 5414 preterm deliveries, found that 26% showed evidence of compromise of uteroplacental blood supply. Although most came from pregnancies complicated by pre-eclampsia, 38% were not, suggesting that preterm delivery may be the *only* abnormal outcome of a pregnancy complicated by reduced uteroplacental blood flow. Steel *et al* (1990) found that those patients with a single abnormal uterine artery waveform at 24 weeks gestation had an increased risk of preterm delivery.

Many studies still use birthweight for gestational age below the tenth or third centile as their definition of IUGR. Altman & Hytten (1989) expressed disquiet about this definition. Miller & Hassanein (1971) used Rohrer's ponderal index (PI) [weight (g) × 100/length (cm)^3] to define asymmetrial IUGR, and found that birthweight by itself is not a valid measure of fetal growth impairment. In our study of 2508 consecutive births, we found that infants with a low ponderal index had higher rates of fetal distress and caesarean section delivery than infants with low birthweight (Fay *et al* 1991). As previously reported, many of the infants with a low ponderal index and a poor obstetric outcome actually had a birthweight in the normal range (Villa *et al.* 1990).

Methods of early detection and management of disease can only be assessed properly if accurate endpoints are used. Bewley *et al.* (1991) define outcome as: birthweight < 10th centile, *or* PIH, *or* APH of any cause, *or* intrauterine death of any cause *or* an operative delivery for fetal distress. Severe outcome is defined as: birthweight <3rd centile, *or* severe proteinuric hypertension, *or* placental abruption, *or* intrauterine death of any cause. The former definition is inadequate and the latter incomplete. Without taking into consideration all the possible outcomes, there will be false positive tests and it may be misleading to assess specificity when incomplete and inaccurate measures of adverse outcome are used. They aimed for a high specificity and to obtain this, set a very high level of resistance index for their definition of an abnormal study, resulting in only 5·8% of their patients having a positive test. This gave many false negative results (74% for primigravid proteinuric hypertension) and a poor sensitivity performance of their test. They could have emphasized the high degrees of sensitivity obtained by using the most abnormal waveform ('worst' RI >0·58), whilst accepting a reduction in specificity. Their result of 82% sensitivity for 'worst' RI (>0·58) in predicting proteinuiric hypertension compares favourably with that of 63% obtained by Steel *et al* (1990) who also used the most abnormal waveform obtained.

By reducing the sensitivity of the test in favour of a high specificity they have devalued a potentially useful tool for the early identification of the 'at risk' pregnancy. Such a move could be justified if any resultant intervention was extreme, but in this case more intensive monitoring of the pregnancy would be the usual course. In this case, high sensitivity is the most clinically useful test characteristic.

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Author's reply

Dear Sir,

We made a careful study of the potential value of uterine artery Doppler studies for screening that precisely measured its predictive properties.

The four outcomes quoted were examined, and more. We investigated separately the relation of uteroplacental resistance index (RI) to three grades of small-for-gestational-age (SGA) babies, mild, moderate and severe proteinuric and non-proteinuric hypertension, four types of antepartum haemorrhage, three indices of fetal distress, ten other pregnancy outcomes including preterm birth, and five different combinations of the above. All these outcomes were examined for eight cut-offs and three different versions of RI. The abnormal waveforms were not rigidly defined (Table 4 showing the results for eight different cut-offs). High sensitivity was not sacrificed for specificity—the test is not yet acceptable for routine use whatever the level of cut-off, whether chosen for high specificity or high sensitivity. There was no reason to emphasize the 82% sensitivity of predicting proteinuric hypertension at a cut-off that generated a specificity of only 36%. In a routine population, 64% of women would be incorrectly identified as being 'at-risk' and 18% of pre-eclampsia and 23% of 'severe' complications would be missed. It is your correspondent who is overvaluing a test that identifies 66% of the pregnant population as 'at risk' (and thus requiring more intensive monitoring) whilst still missing 20% of those with disease.

The combined endpoints of adverse pregnancy outcome were neither inaccurate nor incomplete There was a relation between high RI and SGA, proteinuric hypertension, abruption and elective caesarean section at <37 weeks. Adding elective section at <37 weeks to the combinations did not change the predictions. We found no relation between high uteroplacental RI and fetal distress or preterm delivery. In fact, spontaneous preterm delivery was related only to a low umbilical RI. Even though the ponderal index is a better discriminator of abnormal outcome (i.e., genuine intrauterine growth retardation) than birthweight centile, (a) we examined the abnormal outcomes of fetal distress, neonatal admission, intrauterine death etc and (b) the screening properties of high RI for hypertension, intrauterine death and antepartium haemorrhage could not have been affected.

The groupings of 'any' and 'severe' complications are completely justified. 'Any' was chosen to represent all complications likely to require hospital admission or investigation and cost. 'Severe' was chosen to represent complications that seriously endangered maternal or fetal life. As far as clinicians are concerned, they are interested in all the adverse outcomes that Doppler screening is able to predict for this individual woman's pregnancy.

Uteroplacental RI has many false negatives and false positives. As discussed at length in the original paper, there are a host of reasons that the predictions were not more accurate. We are not disappointed, as the study gave powerful support to the concept of a unifying underlying pathtolgy of 'uteroplacental complications'— pre-elampsia, growth retardation and abruption, detectable by Doppler. RI alone may not be the best Doppler index. We have been able to improve sensitivity without a decrease in specificity by using the early diastolic notch (Bower & Campbell, unpublished) and have also shown improvements in prediction by combining Doppler and placental function tests (unpublished observations).

Susan Bewley
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The prevalence, aetiology and clinical significance of pseudosinusoidal fetal heart rate patterns in labour

Dear Sir,

Murphy *et al* (1991) have contributed to our understanding of factors which may be responsible for the appearance of pseudosinusoidal fetal heart rate (FHR) patterns during labour. Their Fig. 3 depicts an antepartum fluctuating FHR pattern following acute cord haemorrhage which they classify as a 'major psuedo-sinusoidal pattern' because the long-term baseline variability is not 'uniform or fixed'. We have previously reported a strikingly similar FHR tracing also following acute fetal haemorrhage (Hofmeyr & Sonnendecker 1983a). We classified the pattern as sinusoidal because of our finding in an analysis of published 'sinusoidal' FHR patterns that variation in the amplitude of fluctuations within a single tracing could occur in patterns which in all other respects were true sinusoidal patterns (Hofmeyr & Sonnendecker 1983b). We concluded that the features which most consistently identified true sinusoidal FHR patterns were: (i) a fluctuating FHR pattern; (ii) frequency 2–5 cycles/min, counted from peak to peak; (iii) amplitude >5 beats/min, measured from nadir to peak; (iv) markedly reduced short-term variability; (v) rounded peaks and (vi) reduced or absent fetal movements.

Fluctuating FHR patterns which resemble the sinusoidal pattern occasionally occur in the presence of placental abruption with fetal distress. The frequency, however, is invariably below two cycles/min as the fluctuations are related to uterine contractions. Despite their ominous signficance, these should not be called sinusoidal patterns as they appear to represent a completely different pathophysiological process (Hofmeyr & Sonnondecker 1983c).

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Murphy K. W., Russell V., Collins A. & Johnson P. (1991) The prevalence, aetiology and clinical significance of pseudo-sinusoidal fetal heart rate patterns in labour. *Br J Obstet Gynaecol* **98**, 1093-1101.

Authors' reply

Dear Sir,

We thank Drs Hofmeyr and Sonnendecker for their interest in our paper on pseudo-sinusoidal FHR patterns in labour. Their comments are helpful. There is no doubt that the pattern associated with antepartum umbilical cord haemorrhage depicted in Fig. 3 is difficult to classify, but we have opted for the pseudo-sinusoidal classification because we wished to retain the concept of fixed, uniform long-term baseline variability in the definition of the sinusoidal FHR pattern, as proposed by Modanlou & Freeman (1982). We would argue that this is an important part of the definition of a true sinusoidal FHR pattern, and that the smooth, undulating waveform of fixed amplitude, resembling a sine wave, is the pattern which can be most readily identified as sinusoidal by the clinician. The fluctuation in the amplitude of the oscillations depicted in our Fig. 3 means that the pattern does not comply with this definition. We suggest that patterns which demonstrate major fluctuations in the amplitude of the oscillations are typically associated with acute fetal haemorrhage, and may have a different pathophysiological mechanism than true sinusoidal FHR patterns. We speculate that increased baroreceptor activity secondary to blood pressure changes may be an important factor in the pathophysiology of the former pattern whilst a chronically low arterial $P\mathrm{o}_2$ may be critical for the latter.

Regarding the definition of sinusoidal FHR pattern proposed by Drs Hofmeyr & Sonnendecker, we would therefore differ on point (i) and would also add that 'an absence of FHR accelerations and any areas of normal FHR baseline variability' would be preferable to 'reduced or absent fetal movements' in point (iv).

We agree completely with Drs Hofmeyr & Sonnendecker about the pathophysiology and the ominous clinical significance of the pseudo-sinusoidal FHR pattern associated with placental abruption. We believe that this pattern represents recurrent late decelerations from a baseline FHR with absent long-term variability. We too have observed this pattern in association with placental abruption and a 'rippling' pattern of uterine activity. It constitutes an important addition to our paper.

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References

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Emergency cervical cerclage

Dear Sir,

We read with interest the paper by MacDougall & Siddle (1991). However, there are few points not mentioned in the paper that, we believe, are of prime importance in the assessment of this form of intervention. First of all, there is no mention of the mode of presentation of the patients. If they had no uterine contractions, rupture of membranes, vaginal discharge or bleeding, it is difficult to imagine how they presented to the obstetrician. Secondly, in the table, the authors mentioned the age of each patient (which is of little relevance in such cases), but fail totally to mention her past obstetric history, a factor of utmost importance in the diagnosis of cervical incompetence (McDonald 1980).

Their study is retrospective, and suffers from the drawback that there is no control group to assess the value of the intervention. The most it can achieve is to draw attention to the potential value of their technique and direct future research. For them to 'doubt whether it would be ethical to investigate this technique by a randomized controlled trial' is most alarming and reminiscent of our old and regrettable attitude towards routine intrapartum electronic fetal monitoring and the routine use of ultrasound (Lilford & Chard 1985). Finally, for them to conclude that 'there appears to be little hazard to the woman' based on their limited experience with 19 cases is in total disagreement with the literature which cites complications ranging from laceration and sepsis to fistula, uterine rupture and maternal death (Grant 1989).

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Author's reply

Dear Sir,

Thank you for the opportunity to clarify some issues surrounding our recent paper (MacDougall & Siddle, 1991). Sharif & Gee question the manner of presentation of these patients, whether the management of this problem should be investigated by randomized control study and question whether we are aware of the possible risks of cerclage procedures

We reported our experience of attempting to salvage pregnacies that would otherwise have been regarded as inevitable miscarriages, because we believe, first, that this small but important group of patients is not recognized by many colleagues and second, that the potential value of emergency cerclage, described many years ago for the first time by McDonald (1957) was no longer part of the common body of knowledge of obstetricians practising in the United Kingdom. We also hoped to shed some light on why this procedure might sometimes fail and to report some minor modifications of technique

Sharif & Gee report no experience of their own, suggesting that they recognize no such group of patients in their own practice and implying that, previously, they would not have considered a rescue procedure. It is pleasing that our assumptions about the need for publication are thus demonstrated to be correct. We are not surprised to receive such a letter, as a 5-year cohort of junior obstetricians in Bloomsbury have responded with equal incredulity when they have met this management for the first time.

Detecting this group of patients requires careful clinical observation and a positive attitude towards fetal salvage in the midtrimester. Because conventional practice is that such patients are often treated as gynaecological cases and because most junior staff seeing these patients for the first time believe that no salvage is possible, pregnancies between 18 and 24 weeks with advanced cervical dilatation will usually be lost. When cervical dilatation is advanced there is frequently a bag of membranes in the vagina (an hour-glass amniotic cavity). Injudicious vaginal examination often leads to membrane rupture or it is assumed that the most appropriate management is to rupture the membranes and allow this 'inevitable' delivery to take place.

When such pregnancies are managed on a labour ward and a positive attitude is taken towards fetal survival the situation changes. The pregnancies divide into two clear groups: those with infective and haemorrhagic complications and in labour and those who appear merely to have cervical dilatation. The first group are delivered rapidly but the second, if managed conservatively, may well linger for hours or even days before delivery. The number of such patients is small so collective experience is minimal, nonetheless, most experienced obstetricians will have occasional and anecdotal experience of women with advanced cervical dilatation who have taken a surprisingly long time to miscarry.

Where there are several possible courses of action and one is not demonstrably better than another a randomized controlled trial is appropriate. In this particular situation there are two objections to a randomized controlled trial. First, the number of these cases is small and therefore recruitment would prove extremely difficult even on a multicentre basis. Second we are certain, and Sharif & Gee do not contest, that if untreated, women between 18 and 24 weeks with advanced cervical dilatation will inevitably lose their pregnancies. If conservative management, such as the use of tocolytic agents or prolonged bed rest, were associated with a significant degree of fetal survival, a randomized trial could compare the effects of rescue-cerclage versus conservative management on pregnancy outcome and maternal morbidity. However, we believe that these women are faced with certain fetal death or a significant possibility of fetal salvage. Faced with a rare and catastrophic obstetric complication McDonald (1957) and subsequently others, including ourselves, have found rescue cerclage practical and effective. All reported series have shown a greater than 50% salvage in an otherwise hopeless situation A randomized clinical trial is not a nostrum for all clinical problems and until Sharif & Gee can identify an alternative with something approaching the same possible success no ethics committee would sanction a study.

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Early amniocentesis: alphafetoprotein levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 13 weeks

Dear Sir,

I read with interest the article by Wathen *et al* (1991) which emphasized the highly different nature of fluid obtained from the amniotic cavity as opposed to the extra-amniotic coelomic space.

Their study was carried out on 105 apparently normal pregnancies between 8 and 13 weeks. My first comment is that the authors have put forward their results as normal values. Was it possible to confirm the normality of the fetuses after termination or was the material not suitable for pathological examination. Secondly, our main indication for early amniocentesis in Belfast is to obtain cells for fetal karyotyping—did the authors attempt cell culture from the fluid samples in each space and if so, what was their success rate?

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Wathen N. C., Cass P. L., Campbell D J, Kitau, M. J. & Chard T. (1991) Early amniocentesis. alphafetoprotein levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 13 weeks. *Br J Obstet Gynaecol* **98**, 866-870.

Author's reply

Dear Sir,

This study was carried out on apparently normal pregnancies. The criteria for normality were: a singleton pregnancy; the absence of vaginal bleeding during pregnancy and the confirmation by ultrasound scan of a viable intrauterine pregnancy with a normal first trimester appearance and a normal yolk sac.

All of the pregnancies in the study underwent suction termination in the first trimester. Pathological examination of the fetuses was not possible and cytogenetic analyses were not carried out.

Given that this was an unselected group, the chance of a fetal abnormality which would distort amniotic fluid AFP levels would be very low. The incidence of neural tube defects is around 1:300 and that of gastroschisis/exomphalos 1.3000. The chance inclusion of a single abnormal sample would have had little effect on the median value. However, we would agree that before AFP levels can be used for diagnostic purposes in the first trimester, analysis of an appropriate sample of both normal and abnormal pregnancies is required.

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Is Stage I epithelial ovarian cancer overtreated both surgically and systemically? Results of a five-year cancer registry review

Dear Sir,

Finn *et al.* (1992) in their study of stage I ovarian cancer found that adequate staging had been reported in only 30%

It is disturbing but not surprising that cancer registry data highlighted the inadequacy of staging procedures for ovarian cancer performed as defined by FIGO. In South-East Thames, protcols for the diagnosis and management of ovarian cancer were developed by consensus and distributed in 1988. Subsequently, a prospective audit in seven district health authorities has revealed the quality of staging procedures, in 132 ovarian cancers that occurred in 1991, in relation to these protocols. Overall, 61% of notes had a stage mentioned and this varied by 3-month period over the audit from 51% in the first quarter to 27% in the final quarter! Only 42% had a pre-operative chest x-ray, 14% a barium enema. At operation, 40% had no mention of the size of tumour and 92% no mention of residual tumour. There was evidence in only nine that lymph nodes had been sampled, which brings into question the usefulness of stage IIIc (in the FIGO classification requiring lymph node findings) in clinical practice. Although protocols provide guidance and audit results of a surgeon's practice, more is required to improve the adequacy of staging.

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Finn C. B., Luesley D. M., Buxton E. J., Blackledge G. R , Kelly K , Dunn J. A. & Wilson S. (1992) Is Stage I epithelial ovarian cancer overtreated both surgically and systemically? Results of a five-year cancer registry review. *Br J Obstet Gynaecol* **99,** 54-58

Fetal heart block associated with maternal anti-Ro (SS-A) antibody—current management. A review

Dear Sir,

I read with interest the review article by Oláh and Gee (1991) describing the current management of a fetal heart block associated with anti-Ro (SS-A) antibody.

The authors have not mentioned one factor responsible for the development of complete congenital heart block, namely idiopathic familial heart block. This is well recognized (Camm & Bexton 1984) and heart block has been detected in the parents of affected siblings (Lynch *et al.* 1975). However, the proportion of babies with congenital heart block of this type has not been determined even though this has a considerable bearing on pre-conceptional counselling. Furthermore, after the birth of an infant with complete congenital heart block, maternal lupus has been found to be overt in some of the mothers later in life (Kasinath & Katz 1982). This must not be overlooked, and management should include informed counselling of the mother.

I would agree with the authors that there is a strong association between idiopathic complete congenital heart block and anti-Ro and/or anti La (SS-B) antibodies but there are data that suggest that other maternally derived antibodies may often be involved in the pathogenesis of his condition. In addition to anti-Ro antibodies, an unexpected elevation of antibodies to cytomegalovirus can also be found in the mothers of infants with idiopathic complete congenital heart block, suggesting that there may be a virus infected fetal cell against which antibody develops (Taylor *et al* 1986). Thus optimum management has not yet been determined as sometimes maternal derived (anti-Ro) antibodies may be falsely implicated in idiopathic complete congenital heart block.

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Author's reply

Dear Sir,

We would like to thank Dr Dave for showing an interest in our article dealing with fetal heart block.

He alludes to a factor responsible for the development of complete congenital heart block but does not specify what this factor is. The paper cited to support his statement (Camm & Bexton, 1984) is a short review addressing the problem of congenital heart block in adults as a contra-indication to professional pilot status. Having read this paper, we can see no relevance to the subject of our article, nor are we sure what additional aetiology he is trying to draw our attention to.

Regarding the family history of the condition and the latent onset of connective tissue diseases in the mother, these points are adequately addressed in the first and second paragraphs of our paper, and would suggest that Dr Dave refers back to our original article.

The association with cytomegalovirus antibodies is interesting, but is of limited value in a paper intended to address the problems of current management. The paper cited (Taylor *et al.* 1986) shows that the cytomegalovirus serology is an associated factor, but is not necessarily causal Therefore it would be wrong to cite it as an aetiological factor at this time.

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Randomized trial of amniotomy in labour versus the intention to leave membranes intact until the second stage

Dear Sir,

We hope that the paper by Barrett *et al.* (1992) will help to dispel the dogma of routine early amniotomy in all labouring women. This large study suggests that artificial rupture of the membranes does not significantly alter the overall duration or outcome of labour as believed previously (Stewart *et al* 1982, Schwarcz & Caldeyro-Barcia 1982). The increased epidural rate also suggests that labour is probably more painful after this procedure.

Many obstetricians artificially rupture membranes to screen for meconium and to monitor the fetus directly. However, meconium can be present in up to 15% of term pregnancies and correlates poorly with long term neonatal outcome (Yeomans *et al.* 1989) Meconium, in the absence of cardiotocographic abnormalities in a low risk term pregnancy, is more likely to be caused by vagal stimulation in a mature fetus than by 'fetal distress'

Keirse *et al.* (1981) showed high consistency in baseline variability and decelerations between ultrasound and fetal scalp electrode cardiotocographic recordings, and that the former would not present an over optimistic interpretation of fetal health. Internal monitoring offers little extra advantage if a good quality external cardiotocograph has already been obtained.

As such, routine amniotomy in low risk labours (which constitute 70% of pregnancies) should be abandoned. This should be reserved for abnormal labours where progress is suboptimal or where external monitoring shows fetal heart rate abnormalities. We suggest that there is a place for rupturing intact membranes at full dilatation so that adequate measures can be taken should the meconium appear unexpectedly.

In general, unit policies on artificial membrane rupture do not cater for the wishes of the mother (Henderson 1991). In a low risk labour that is progressing well, it is reasonable to allow the mother the choice of amniotomy or keeping the membranes intact, our role as professionals being to ensure that she has unbiased information on which to base her decision. The indiscriminate use of such an invasive procedure, that is associated with potential hazards such as sepsis, haemorrhage and cord prolapse, and is of little proven benefit, is not justifiable.

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British Journal of Obstetrics and Gynaecology
June 1992, Vol. 99, pp. 533–536

BOOK REVIEWS

Aids and Human Reproduction. First International Symposium AIDS and Reproduction, Genoa, 1990 edited by F. Mélica. Karger, Basel, 1992, 196 pages, with figures and tables, SFr 169, DM 202, £73.50, US £135.25

Aids and Human Reproduction covers a facet of the problems of HIV infection that is of increasing importance. Like all conference proceedings and resulting publication tends to be a little disjointed. Within the introductory section on epidemiology the papers on antenatal testing are the most pertinent. Inevitably, heterosexual transmission receives considerable attention and the comparisons of drug abusing and non-drug abusing populations are important. There is a discussion on the prospects for pre-natal diagnosis of congenital infection with HIV utilizing fetal blood sampling—a technique whose safety in this context is not clearly established. Two papers address the question of therapy for HIV infected women. There are at present insufficient data on which to base a decision on the role of zidovudine.

There are papers on human papilloma virus infections and cervical intra-epithelial neoplasia in association with HIV and some discussion of the potential for assisted reproductive techniques to enable HIV infected parents to produce HIV-free offspring. One paper indicates that spermatazoa themselves may contain HIV particles in men with AIDS.

The book ends with some papers on the ethical-legal situation surrounding HIV infection and pregnancy, and a review of the hazards to health care workers in the specialities in which uncontrolled blood contamination is a common feature.

This is a useful reference work for those with a specific interest in the topic and for all specialists in the field. It could usefully be placed in departmental libraries but at £73.50 must be considered expensive for its size.

C. N. Hudson

Fetal and Neonatal Physiology Volumes I & II edited by Richard A Polin & William W. Fox. W. B. Saunders Co., Philadelphia, London, Toronto, 1992. Vol. I 938 pages, Vol. II 1884 pages, with figures and tables, £200 the set

For many years, knowledge of the physiology of early development has been related, primarily, to care of the newborn infant. However, developments in basic scientific methods and non-invasive technology over recent years have begun to allow an understanding of fetal physiology to be derived from experimental and clinical practice. *Fetal and Neonatal Physiology* claims not to be a clinical text but an in-depth exposition of basic physiology, together with relevant genetics, embryology and pharmacology, of the fetus and neonate. This ambitious project has harnessed the talents of 383 contributors into a textbook comprising two large volumes (total 1884 pages) of attractive appearance and high quality presentation. Unfortunately, the excellent standard of individual contributions has not been matched by the selection of topics and organizations of the contents

It is the stated aim of the editors that almost every chapter contains discussion of 'normal' adult physiology as well as a description of the physiological differences that exist in the fetus and neonate. Sadly, this objective has not been achieved. Apart from a few topics, it remains for different sections and individual chapters separately to tackle different aspects of pre and postnatal physiology. Twenty-eight sections contain the 190 chapters that comprise this large textbook. The vast majority (232) of the contributors are based in the USA but the remaining 51 come from 11 other countries. However, the number of physiologists contributing is rather low, which may indicate how little this subject has been taken up by basic scientists.

Although the book appears to present the subject matter more in the manner of a basic than a clinical textbook, the resultant format, whereby several chapters contribute to each section, produces a mixture of the two. In this manner the book attempts to give clinical relevance to the basic science. The chapters have been organized into sections which each address a specific area, such as: placenta, growth, metabolism, thermoregulation, circulation, lungs, gastrointestinal tract, liver, kidney, blood, fluids and electrolytes, immunology, neurology, orthopaedics and endocrine glands. The order of the sections seems arbitrary and the selection of chapter topics to provide coverage of each area is far from uniform in its approach. For example, blood flow in the fetal and neonatal liver, kidneys and brain are discussed in the sections relating to the respective organs whilst the sections on lung, gastrointestinal tract, and endocrine glands do not contain chapters on blood flow. Chapters vary enormously in length and their scope appears to be far too great for many of the contributors. Apparent lack of editorial direction has allowed many of the chapters to appear without an obvious structure—the contributions are neither historical, explaining how advances in techniques have improved understanding, nor are they conceptual, as would be expected of most state-of-the-art reviews. Lack of uniformity is also evident with the references which are largely in a 'writer friendly/reader unfriendly' style listed according to order of citation in the text. This limits the readers' ability to scan the reference lists for particular authors and makes the job of looking for particular references very tedious. The omission of 'suggested further reading' lists is also a serious flaw in a book with so many references. New students require reference to other recent reviews in order to obtain a balanced opinion before undertaking in-depth literature searches in an area of interest.

The combination of fetal and neonatal physiology in one text is a laudable and logical objective. The stated purpose is to provide a clear understanding of the physiology, which it does, even though the lack of uniformity of organization of the sections makes the use of this book as a reference manual rather difficult. It is impossible to predict where many topics will appear and the fact that the index is no better than average means that the reader will come across many topics by surprise. Perhaps this is what the editors mean by intending the work to be a 'readable', in-depth, presentation of fetal and neonatal developmental physiology.

The subject of perinatal physiology is changing so rapidly that it remains a puzzle as to how a textbook as large as this can be justified. The target audience cannot be the busy undergraduate studying fetal physiology or working on obstetric or paediatric firms. Neither is it suited to the young postgraduate revising for his specialist exam. Perhaps it is for teachers who like to have a large, ready-made, data base to hand. Perhaps researchers in the field will use it as a source book for areas about which they are ignorant. However, books like this suffer two fatal problems with respect to being considered authoritative. They are out of date by the time they reach the bookstore and selection of references by contributors will always be subject to personal bias. Although this textbook brings together the physiological wisdom of a large number of workers, mainly clinicians, eminent in the field of perinatology, we cannot believe that many individuals will decide to, or be able to, purchase this book. It is appropriate for libraries in teaching establishments and will remain a testament (or perhaps a monument) to the level of physiological understanding of the fetus and neonate in 1992

John A. D. Spencer
Mark A. Hanson

Diffusion Four Screening Tests Across Europe (A Study of the Diffusion of Medical Technology in Europe), edited by Margaret Reid. Available from The King's Fund Centre for Health Services Development, 126 Albert Street, London NW1 7NF, 1991, 133 pages, £9.95.

Major scientific innovations which are eventually manifest in screening techniques often appear to have spread into medical practice by osmosis This is patently not true. There are complex interactions between public health planners, doctors and the consumer (in this case pregnant women), and these must be arranged like a human pyramid on the scientific foundations and technology of the tests themselves.

Screening for genetic and cytogenetic disease in pregnant women, where the endpoint of a positive test may be the termination of a wanted pregnancy, is still one of the most controversial aspects of medicine today The author shows how prenatal screening has developed with different governmental, legal, medical, genetic and religious backgrounds and that policies in Britain are by no means uniform. By including chapters on the development of screening in Germany, Sweden, Greece and Spain by guest authors from these countries, the wide regional, national and international differences and the backcloths against which policies in each country were developed are shown. Finally, there is a section by the editor of the series, Barbara Stocking, on innovation, adoption and diffusion of medical technology in European countries.

The indications for sampling, the techniques used, public support, abortion law and temporal changes over the past 20 years have all affected uptake rates. The negative legacy of the Nazi regime in Germany, particularly with regard to abortion law, can be contrasted with the more liberal background prevailing in Sweden. However, for all the efforts to effect rational and effective screening policies, it is interesting to examine the extent to which this has affected the ways in which screening is available to women at risk. For example, the uptake of invasive testing (amniocentesis or chorionic villus sampling) for Down's syndrome in older mothers is principally among those women with higher levels of education who reside in urban areas and attend younger physicians (whose risks are no greater than those of comparable age and similar obstetric history, but who have less education, older obstetricians and live in the country).

There are drawbacks to producing a book which examines polices in fast moving and rapidly changing fields. This book was published in 1991, but during the time it was in preparation, there were major changes in prenatal screening policies. The book thus gives a rather dated impression, because the changes have dramatically altered screening policies in the face of the risks of invasive sampling using chorionic villus sampling and the advent of maternal biochemical screening for Down's syndrome in younger women. The emergence of controversy about the applicability of chorionic villus sampling for older mothers because of fetal loss rates, diagnostic accuracy and reports of oromandibular-limb hypogenesis syndrome occurring in pregnancies where CVS was carried out before 9 completed weeks of pregnancy occurred during the book's gestational period. The discussion of maternal serum AFP is principally in relation to the use of elevated levels in the detection of neural tube defects. Only a single final paragraph is devoted the use of low maternal serum AFP levels (or triple testing using AFP, oestriol and hCG) to screen for trisomies. AFP screening for Down's syndrome has been a major innovation in antenatal care. Regions which had not been using AFP screening because they felt cost-effectiveness could not be justified for neural tube defects alone have changed their policies now that AFP measurement can be used both for neural tube defects and Down's syndrome screening.

It is unfortunate for the author that some of the more dramatic and far-reaching changes in prenatal screening policies have occurred during the period when the book was being written. This does not diminish the interest and insight which this book provides in the descriptions of attempts to improve the quality of healthcare, and the ethical problems and social impact of these measures against the ever-increasing cost of these new technologies.

Christine Gosden

The Biology, Development and Care of Twins, Triplets and More. A video produced by The Multiple Births Foundation, Queen Charlottes & Chelsea Hospital W6 0XG, 34 minutes, £25 (£20 to members of MBF)

Twins and multiple births are on the increase. 1:45 women now give birth to twins and 200 sets of triplets were born in 1990. Dr Elizabeth Bryan, Medical Director of the Multiple Births Foundation introduces this video and emphasises the importance of raising the awareness of professionals to the special needs of parents and children of multiple births.

Topics form short sections and cover the biology of twinning, zygocity, causes of twinning, diagnosis and pregnancy, feeding and the first years, higher order births, a twin with a disability, bereavement and where to find help.

The section on zygocity is diagrammatically presented and easy to assimilate and the other topics are enhanced by having parents with multiple births discussing and highlighting specific areas of need in their experience. I found the couple talking about their bereavement of one twin especially moving.

Mode of delivery is not addressed due to the variation in obstetric views on the subject although this must have some consequence for appropriate professional care Working as I do in the inner city, I should have liked some discussion on the effect of socio-economic and racial background on the availability of support for some families.

The topic of multiple births is obviously immense and cannot be covered in 34 minutes but this video manages to raise one's awareness in many areas. A very useful training tool and trigger film for all those involved in maternity and community care.

Lizzie Hibbitt
Health Authority
Parkside

Diabetes in Pregnancy. Baillières Clinical Obstetrics and Gynaecology, Volume 5, No. 2, edited by J N. Oats. Ballière Tindall, London, 1991, pages 257–509, £27.50

Pregnancy complicated by diabetes has at last been granted more than a single chapter in this review serial. The editor notes, probably wisely, that several excellent and comprehensive books on this subject have appeared recently. He suggests this volume will highlight particular aspects of the subject for practitioners who may not be deeply involved in what he calls 'this subspecialty'.

Pearson's review of the inheritance and development of insulin dependent diabetic mellitus is comprehensive. Kuhl's chapter on the aetiology of gestational diabetes reviews the work of his own group in detail, but might seem too specialized for the target audience, especially with so little content about the epidemiology of gestational diabetes and its relation to diet, and obesity and age.

Coustan picks his way carefully through the minefield of 'screening and diagnosis ofgestational diabetes'. He highlights the many areas of potential confusion for the unwary. Combs & Kitzmiller contribute an excellent review on miscarriage and congenital malformation. Langer's chapter on prevention of macrosomia could have been clearer. The omission of any reference to the work of Weiss' Austrian group on 'target-oriented insulin therapy' is in my opinion unreasonable. The non-expert might also prefer a clearer separation of the management differences presented by insulin dependent and gestational diabetes. The next chapter is an interesting contribution by Hare on the effect of pregnancy on women with complicated diabetes

Hadden on the medical management of diabetes covers again much of the subject matter on diagnostic criteria in Coustan's earlier chapter. His proposals for management are, as he admits, didactic, and it is a surprise that the dietician find no place in his multidisciplinary management team.

The editor's chapter on obstetrical management touches on most relevant questions. (Steel and her colleagues in Edinburgh might be surprised to find he has located their unit in Aberdeen.)

Mountain's chapter on the infant of the diabetic mother is an excellent comprehensive review accompanied by sound management advice

Cousins reports the massive California Diabetes and Pregnancy Programme (CDAPP). This is a multicentre prospective study of a prescriptive programme for the care of pregnant diabetics. It seems to me to have missed a wonderful opportunity for a series of randomized trials of management strategies. The author is reduced to trying to assess the programme's results in comparison with, historical controls, other published series and non-diabetic women

Henry & Beischer contribute an interesting review of their follow-up studies of women diagnosed as gestational diabetics It is good to note that their subjects and controls are enrolled in long-term follow-up.

Van Assche and colleagues examine the animal and human evidence in the vertical transmission of gestational diabetes. The final chapter is from Skouby and colleagues on contraception for women with diabetes This is an excellent review and includes the controversy over the effectiveness of the IUCD.

Overall, it is hard to recommend this book. The contributions are of variable quality and not presented in any logical sequence. The non-expert might prefer one of the smaller standard textbooks and the expert will probably do better to save his money a little longer and purchase the recent American book from Reece & Coustan, reviewed in these columns in 1989 (96, 4, 503).

Robert Fraser

Fetal and Neonatal Effects of Maternal Disease, edited by Avron Y. Sweet and Edwin G. Brown. Mosby Year Book 1991, St Louis, Baltimore, London, 463 pages, with figures and tables, £55.00

'There are many excellent texts devoted to the subject of diseases of the pregnant woman but precious little organised information has been compiled concerning the consequences to the fetus and neonates '—thus the preface to this book justifies its existence. I take issue with that statement. I think there are many excellent texts which deal with the inseparable implications for mother and baby of maternal illness in a much better way than this book does.

Given this underlying philosophy, and the fact that only four of the 28 contributors are obstetricians, it is not surprising that the coverage of the subject material is patchy and inconsistent to say the least. For example, the chapter on hypertension and pre-eclampsia is well balanced with an excellent discussion on the pathophysiology of the disease and its effects on the mother, the fetus and the newborn Management implications for the fetus and newborn are also well presented. In contrast, the chapter on haematological and hemorrhagic diseases makes no mention of alloimmune thrombocytopenia purpura—presumably because it is not a maternal 'disease'. Similarly there is no mention of neonatal risks and management in the section on rhesus isoimmunization. Some chapters discuss management, others do not, concentrating solely on risk.

A striking feature of the book which is in part responsible for this inconsistency is that it is really two books Of its total length (463 pages) nearly half (213 pages) is taken up with five chapters on maternal infection of various types. All other maternal illnesses are crammed into twelve chapters Thus, by and large, the infectious diseases are dealt with well whereas the other, and arguably more important, conditions suffer from this arrangement.

In summary, would I recommend the book? For its section on infectious diseases at a price of £55.00, I would suggest it would be a useful acquisition for a library. However, I have doubts about the value of the remainder of the text. For paediatricians, the maternal and fetal aspects covered are incomplete and inconsistent.

However, obstetricians may find the neonatal coverage a useful adjunct to their counselling of women with illness in pregnancy.

D. K. James

Exercise in Pregnancy, second edition, edited by Raul Artal Mittelmark, Robert A. Wiswell & Barbara L. Drinkwater. Williams & Wilkins, Baltimore, 1991, 332 pages, with figures and tables, £43.00

The second edition of this book is comprehensive and well produced and makes a worthwhile contribution to the literature of the physiology of human pregnancy There are three main sections—eleven chapters on physiological adaptations to pregnancy, eight on the physiology of exercise in pregnancy, and nine on practical applications.

Chapter 8 by Girandola and colleagues consists of a brief but useful, critical analysis of techniques for measuring body composition and their value in the pregnant subject.

In Chapter 9 the recommendations of the Food and Nutrition Board of the American National Research Council of an extra 300 calories per day of energy intake in pregnancy are accepted uncritically. The authors then go on to suggest that physically active women need even more extra calories in relation to the amount of exercise This is despite the authors' knowledge of recent work suggesting adaptation in energy conservation in pregnant women and non-pregnant women indulging in regular exercise—studies referred to in the introduction to their chapter.

Chapter 12 on exercise physiology by Wiswell is an interesting critical article central to the text and Clapp makes a succinct contribution on maternal exercise performance and early pregnancy outcome There are useful reviews on pregnancy in the elite and professional athlete, by Hale & Mittelmark, and on work and exercise during pregnancy by Hatch & Stein.

Mittelmark and colleagues' chapter on the effect of maternal exercise on pregnancy outcome includes the following sentence: 'Based on the present published literature, it is not possible to conclude in a scientific way whether maternal exercise is beneficial or detrimental in pregnancy.' This should be reassuring to both the sedentary and the active gravida—and a stimulus to research for medical scientists.

Robert Fraser

Books received some of which may be reviewed at a later date

Pregnancy, Diabetes and Birth: A Management Guide Second edition, edited by Dorothy Reycroft Hollingsworth. Williams & Wilkins, Baltimore 1992, 288 pages fully illustrated, £54.00

The Menopause and Hormonal Replacement Therapy. Facts and Controversies, edited by Regine Sitruk-Ware & Wulf H. Utian. Marcel Dekker Inc., New York, 1991, 320 pages fully illustrated, $99.75 (US and Canada), $114.00 (all other countries)

Primary Care of the Preterm Infant edited by Judy C. Bernbaum & Marsha Hoffman-Williamson. Mosby Year Book, St Louis, Baltimore, Boston, 1991. 344 pages, fully illustrated, softcover £25.50

Colporoctology and the Pelvic Floor Second edition, edited by M.M. Henry & M. Swash. Butterworth Heinemann, Oxford, 1992, 499 pages, fully illustrated, £95.00

Vaginitis and Vaginosis edited by Benson J. Horowitz & Per-Anders Mardh. Wiley-Liss, New York, Chichester, Brisbane 1991, 274 pages with figures and tables, $59.95

Recent Advances in Obstetrics and Gynaecology No 17 edited by John Bonnar. Churchill Livingstone, Edinburgh, London, Melbourne, New York, 1991, 244 pages, illustrated £22.50

Aids to Obstetrics and Gynaecology for MRCOG Third edition by Gordon M. Stirrat. Churchill Livingstone, Edinburgh, 1991, 306 pages, £10.95

Hormone Replacement Therapy. Your Questions Answered by Malcolm Whitehead & Val Godfree. Churchill Livingstone, Edinburgh, 235 pages, £6.95

International Travel and Health. Vaccination Requirements and Health Advice Situation as on January 1st 1992. World Health Organization, Geneva, 1992, 96 pages Swfr.15.00. Price in developing countries Swfr.10.50

Proceedings and Symposiums

Oral Contraceptives and Neoplasia. WHO Technical Report Series 817. Report of a WHO Scientific Group, World Health Organization, Geneva. 1992, 46 pages Swfr 9.00, in developing countries Swfr. 6.30

Maternal Mortality—The Way Forward. Some implications of the Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985-87 edited by Naren Patel. This book is based upon the Proceedings of a Postgraduate Meeting held at the Royal College of Obstetricians and Gynaecologists in January 1992. Published and distributed by The Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, £7.00

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9th-10th October	**Diplomates' Course for General Practitioners**
28th October	Scientific Meeting **Management of Infertility**
30th November- 4th December	**Consultants' Conference**

Further details can be obtained from:
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27 Sussex Place, Regent's Park, London NW1 4RG
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Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London